DIPLOMARBEIT

The role of nutrition
in the prevention and treatment of dementia

Verfasserin

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angestrebter akademischer Grad

Magistra der Naturwissenschaften (Mag.rer.nat.)

Wien, im Februar 2012

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ABBREVIATIONS

Aß	Beta Amyloid
ARA	Arachidonic Acid
AD	Alzheimer's Disease
ADC	AIDS Dementia Complex
ADL	Activities of Daily Living
αKGDH	α-Ketoglutarate Dehydrogenase
ANH	Artificial Nutrition and Hydration
ApoE	Apolipoprotein E
APP	Amyloid Precursor Protein
ARD	Alcohol Related Dementia
BASE	Berliner Alterstudie
BHMT	Betaine-Homocystein Methyltransferase
BMR	Basal Metabolic Rate
CAA	Cerebral Amyloid Angiopathy
CBF	Cerebral Blood Flow
CBS	Cystathionine Beta Synthase
CHAP	Chicago Health and Aging Project
ChAT	Cholin Acetyltransferase
CJD	Creutzfeld Jacob Disease
CMRg	Cerebral Metabolic Rate for glucose
CNS	Central Nervous System
CR	Calorie Restriction
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
CT	Computed Tomography

DHA	Docosahexaenoic acid
DLB	Dementia with Lewy Bodies
DNMT	DNA Methyltransferase
DSM	Diagnosis and Statistical Manual of Mental Disorders
EdFED	Edinburg Feeding Evaluation in Dementia
EEG	Electroencephalography
EGCG	Epigallocatechin Gallate
EPA	Eicosapentaenoic acid
FAD	Familial Alzheimer's Disease
FTD	Fronto Temporal Dementia
GABA	γ-aminobutyric acid
GbE	Ginkgo biloba Extract
GLUT 1	Glucose Transporter 1
GSH	Glutathione
GSHPx	Glutathione Peroxidase
GSK3ß	Glycogen Synthase Kinase 3ß
GS	Glutathione Synthase
GST	Glutathion S-transferase
HAART	Highly Active Antiretroviral Therapy
HMGR	3-hydroxy-3-methylglutaryl coenzym A reductase
HO-1	Heme Oxygenase
ICD	International Classification of Diseases
IFNs	Interferons
LBD	Lewy Body Dementia
LBM	Lean Body Mass

MAO-B	Monoaminooxidase-B
MAP	Mitogen-activated Protei
MCI	Mild Cognitive Impairment
MCM	Methylmalonyl-CoA mutase
MID	Multi Infact Dementia
MMA	Methylmalonic Acid
MMSE	Mini Mental-State Examination
MNA	Mini Nutritional Assessment
MPP^+	1-Methyl-4-Phenylpyridinium
MPTP	1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
MRI	Magnetic Resonance Imaging
MS	Methionine Synthase
5-MTHF	5-Methyltetrahydrofolate
5,10-MTHF	5,10-Methylentetrahydrofolate
MTHFR	Methylenetetrahydrofolate Reductase
MTR	Methionine Synthase
MUFA	Monounsaturated Fatty Acids
NAD	Nicotinamide adenine dinucleotide
NADP	Nicotinamide adenine dinucleotide phosphate
NFTs	Neurofibrillary tangles
NOS	Nitric Oxid Synthase
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NMDA	N-methyl-D-aspartate
OBS	Organic Brain Syndrome
PARPs	poly(ADP-ribose)polymerases
PC	phosphatidylcholine
PCM	Protein Caloric Malnutrition

PDD	Parkinson's Disease Dementia
PDHC	pyruvate dehydrogenase complex
PEM	Protein Energy Malnutrition
PEG	Percutaneous Endoscopic Gastronomy
PET	Positron-Emission Tomography
PHF	Paired Helical Filaments
PI3K	phosphatidyl inositol 3-kinase
PP2A	Protein Phosphatase-2A
PPMT	Protein Phosphatase-2A Methyltransferase
PSEN1	Presenilin 1
PSMQ	Pfeiffer's Mental Status Questionnaire
PUFAs	Polyunsaturated Fatty Acids
PVS	Persistent Vegetative State
rCBV	relative Cerebral Blood Volume
RCT	Randomized Clinical Trial
RFC1	Reduced Folate Carrier-1
RDA	Recommended Daily Allowance
ROS	Reactive Oxygen Species
SAH	S-Adenosylhomocysteine
SAM	S-Adenosylmethionine
SirT2	Silent Information Regulator Two Protein (Sirtuin)
SIVD	Subcortical Ischemic Vascular Dementia
SGA	Subjective Global Assessment
SLP	Speech-languange Pathologist
SOD	superoxide dismutase
SSRIs	Serotonin Reuptake Inhibitors

TD	Thiamine Deficient
TFA	Trans Fatty Acids
THF	Tetrahydrofolate
TMP	Thiaminemonophosphat
TPP	Thiaminepyrophosphat
UCH-L1	Ubiquitin Carboxy-Terminal Hydrolase L1
WHICAP	Washington Heights-Inwood Columbia Aging Project
WKS	Wernicke-Korsakoff syndrome
WMLs	White Matter Lesions
VaD	Vascular Dementia
VCI	Vascular Cognitive Impairment

1. Introduction

The world population is ageing. At present, people who are born in developed countries now, are expected to live in average more than 80 years, with women living a few years longer than men. With this demographic development, the prevalence of old-age-related diseases, such as dementia, will increase rapidly in the future. Understanding dementia is essential for future public health.

In health care, dementia is characterized by dependency on caregivers. Dementia patients can't perform their daily activities without help from others. They become unable to organize or prepare their own meals; therefore eating and drinking become difficult processes. Nutritional problems then emerge at some time during disease's progression. Such patients are likely to forget mealtimes, have no appetite or even refuse to eat. Malnourishment is frequently seen in this group, as a result of deficient energy intake over a period of years. In the end stage, as the medical condition worsens, tube feeding in the form of PEG (percutaneous endoscopic gastronomy) is often deployed.

This diploma thesis will try to explore ways of establishing the optimal solution for feeding dementia patients, with the primary objective of improving quality of life in its last stages. The first chapter will present background information and outline recent researches into dementia . Following this, there will be a description of nutrients suspected to have a connection with the development of dementia. The next section will deal with nutritional issues connected with psycho-social problems in the middle and advance stages, which may affect the daily lives of the elderly with dementia. Tube and oral feeding are the main topics in the last two chapters. Based on recent studies reported in books and scientific journals, the advantages and disadvantages of each feeding type will be examined. The author is very much aware of the multidisciplinary nature of this issue, and

therefore although nutrition is the main emphasis in these writings, brief survey of the relationship with issues in other fields, such as ethics, law and psychology, will be included in the last chapter. Improvements in nutritional knowledge alone would not mean so much, if decision making as to whether to apply or withhold tube feeding is not supported by suitable social controls.

In the last instance, I would like to thank Prof. Elmadfa, who has lead the way, and to give the opportunity to learn about life from a terminal illness such as dementia and how to see 'the big picture' instead of looking at issues in isolation like small pieces of puzzle. It is hoped this work will be of benefit to all aspects of the treatment and therapy of dementia.

Vienna, February 2012

2. Background

2.1. History of dementia

Descriptions of memory damage in the history of relevant literature can be traced back as far as 400 BC in the writings of Plato and Aristotle [KARENBERG and FÖRSTL 2006]. The term dementia[1] itself, is used by Roman poet and philosopher Lucretius to describe the condition of being out of one's mind [MALGORZATA et al. 2004].

In the 18th century, the term senile dementia was first used in 1798 by French psychiatrist Philippe Pinel in his book Nosographie. His student, Esquirol, then differentiated dementia from amentia[2] and defined dementia as a "cerebral disease characterized by sensibility, intelligence and will impairment" [3][ROMÁN 2002].

Advances in the fields of microscopy, histology, genetics, neuropathology and other areas of medicine in the 20th century contributed to a better understanding of dementia. Dementia today refers to a condition in which there is a loss of cognitive function, caused by brain disorders, severe enough to interfere with daily social and occupational life [MALGORZATA et al. 2004] . Based on clinical presentation, neuropathology and etiology, dementia is categorized further into four major groups; AD, Parkinson's groups, FTD groups and vascular groups [GROSSMAN et al 2006].

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1   The word 'dementa' is derived from latin, *dement-demens*, which means out of one's mind.
2   According to Esquirol, amentia or idiocy is "not a disease, but a conditions in which the intellectual faculties are never manifested or have developed sufficiently to enable the idiot to acquire knowledge"
3   Esquirol also explained a parable comparison between amentia and dementia; "demented person is like a rich man who become poor, meanwhile amentia has always in a state of want and misery"

To date, there still no cure for these diseases, although medication and therapy are provided to slow the progression of the disease and patients in the advanced stages may receive palliative care[4].

2.2. Definition of dementia

According to ICD-10[5], "Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. Impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation."

DSM-IV [6] defines dementia as "multiple cognitive deficits, including memory impairment and at least one of the following disturbance:

– aphasia (language problems, difficult to produce names of individuals and objects)

– apraxis (poor motoric coordination)

– agnosia (fail to recognize objects)

– disturbance in executive functioning, severe enough to cause impairment in daily activity and must show a decline from previously higher level of functioning".

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4   Palliative care is usually applied for patients with life-threatening illness, it aims to improve quality of life through prevention of pain and regards dying as normal process.

5   ICD-10 is International Classification of Diseases published by World Health Organization, current revision is from 2006, comprises definition, classification and diagnosis of diseases, thus provide basis for national statistic

6   DSM-IV stands for Diagnosis and Statistical Manual of Mental Disorders, is published by American Psychiatric Association, 4th edition, 2000

Difference from delirium and other diseases

Some conditions may appear similar to dementia. Age-related cognitive decline, delirium, schizophrenia, and depression develop similar symptoms, that seem to overlap and should be ruled out before dementia is diagnosed. Delirium for example, although also presenting memory impairment as a symptoms, is characterized by disturbance of consciousness and develops over a short period of time, whereas persons with dementia remain alert and progression of cognitive loss takes from months to years. If the underlying illness from other medical conditions or substance abuse are treated, delirium usually can be healed [DSM-IV-TR 2000].

Another disease often linked with dementia is Mild Cognitive Impairment, where impaired memory is the only area affected, while the elderly with dementia show deterioration in other cognitive areas as well [PETERSEN 1999]. Although still curable, approximately 10-15% MCI's patients from certain subtype progress to Alzheimer's Disease, suggesting MCI may be a transition link between normal ageing and dementia [GRUNDMAN et al 2004].

Dementia is a chronic progressive illness, for which to date there is still no available cure, persons with dementia live approximately 2-6 years after the initial onset of symptoms [MITCHELL 2007]. The main causes of death are usually unrelated to dementia, such as pneumonia, cardiovascular disease, and pulmonary embolus [KEENE et al 2001].

2.3. Epidemiology

A Swedish review study investigating the correlation of age and the prevalence of dementia showed, that the prevalence rises with increasing age, double in every 5 years after the age of 65. In the group older than 95, almost half the population developed dementia [SBU 2008]. Incidence also increases with age, both prevalence and incidence data shows no geographic difference, but significant gender distinction. The data for women show a higher prevalence. Even so, gender is not considered a risk factor for dementia, higher life expectancy in women may be attributable here. Figures from EURODEM[7] meta-analyses for European studies show close similarities [HOFMAN 1991].

Age (years)	Prevalence	Incidence (1000p/y)
60-64	1 %	1
65-69	1.5 %	3-5
70-74	3 %	8-10
75-79	6 %	11-18
80-84	13%	24-40
85-89	24%	30-60
90-94	34%	50-120
>95	45%	

Table 1: Prevalence of dementia with increasing age [SBU 2008]..

Along with the growth of an older population, the number of dementia cases is expected to rise fourfold in the next 50 years. According to Alzheimer's Disease International, there were around 35.6 million[8] dementia cases worldwide in 2010, this figure is estimated to nearly double every 20 years.

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7 European Community Concerted Action on the Epidemiology and Prevention of Dementia group, a meta-analysis study from 10 European countries.
8 World Alzheimer Report 2009

Region	Crude prevalence[9]	2010	2030	2050
Worldwide	4,7%	35,56 million	65,69 million	115,38 million
Europe	6,2%	9,95 million	13,95 million	18,65 million
North-and Latin America	6,5%	7,82 million	14,78 million	27,08 million
Asia	3,9%	15,94 million	33,04 million	60,92 million
Africa	2,6%	1,86 million	3,92 million	8,74 million
Austria[10]	1,27%[11]	108.400	163.400	233.800

Table 2: Estimation of dementia's prevalence by regions [World Alzheimer Report 2009]

An enormous rising percentage in incidence is to be expected in low and middle income countries, in 2050, it is estimated 70,5% people with dementia will live there [World Alzheimer Report 2009].

To predict the social burden in the future, Wancata et al calculated a relation between people of a productive working age and persons with dementia in Austria.

Year	People in working age (15 – 64y/o)	People with dementia	Number of working-age people per demented person
2000	3.811.145	90.493	42
2010	4.103.910	108.983	38
2030	4.102.718	165.078	25
2050	3.963.473	269.603	15

Table 3: Ratio people in working age and with dementia in Austria [Wancata et al 2001]

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9   Crude estimated prevalence: % prevalence from population over 60y-o.
10 [WANCATA et al 2001]
11 EURODEM, Austrian Dementia Report 2009 p 14

According to the Austrian Dementia Report 2009, the average annual cost per person in Austria is 12.443,10€ for housecare and 34.887,55€ for care in nursing homes. In average 7 years duration of the disease, the prognosis for the total cost in Austria thereby are 1,84Mrd€ in 2010, 2,69Mrd€ in 2030 and 4,56Mrd€ in 2050 [Austrian Dementia Report 2009].

International data is comparable with Austrian figures, for example, as in the Netherlands 14.854€ per demented person in 2004, Scandinavian countries 17.860,14€ per person with AD in 2006, USA 19.404,55€ per person with AD in 1996 [Austrian Dementia Report 2009].

Recognizing this huge burden in the future, prevention and effective treatment as well as disease management of dementia should have take priority in future research.

2.4. Forms of Dementia

Based on etiology, DSM-IV-TR differentiate types of dementia as follow :

- Alzheimer's Disease

- Vascular Dementia

- Dementia due to other general medical condition

  - Dementia due to HIV Disease

  - Dementia due to Head trauma

  - Dementia due to Parkinson's Disease (Lewy body related neurodegeneration)

  - Dementia due to Huntington's Disease

  - Dementia due to Pick's Disease (focal degeneration in frontal and temporal lobes)

  - Dementia due to Creutzfeldt-Jakob Disease

  - other conditions associated with dementia

    - structural lesion (e.g. primary or secondary brain tumors, subdural hematoma)

    - endocrine conditions (e.g. hypothyroidism, hypercalcemia, hypoglycemia)

    - nutritional conditions (e.g. deficiencies of thiamine or niacine)

    - other infectious conditions (e.g. neurosyphilis)

    - immune disorders (e.g. temporal arteritis, systemic lupus erythematosus)

    - derangements of renal and hepatic function

    - metabolic conditions (e.g. Kufs' disease)

    - other neurological conditions (e.g. multiple sclerosis)

- Substance-Induced Persisting Dementia

  - associated with substance clases : alcohol, inhalants, sedatives, hypnotics and anxiolytics)

  - medications to cause dementia: anticonvulsants, intrathecal methotrexate

  - toxin exposure : lead, mercury, carbon monoxide, organophosphate insecticides and industrial solvents

- Dementia due to Multiple Etiology

•	Dementia not otherwise specified

Table 4: Types of dementia according to DSM-IV-TR 2000

Subtype	Dementia case proportion	Neuropathology	Characteristic symptoms
AD	50-70%	Cortical amyloid plaques neurofibrillary tangles	Impaired memory, apathy and depression, gradual onset
VaD	20-30%	Celebrovascular disease single or multi-infarct	Similar to AD but less memory affected, mood fluctuation prominent, physical frailty, and stepwise onset
DLB	<5%	Cortical Lewy bodies (alpha-synuclein)	Marked fluctuation in cognitive ability, visual hallucinations, tremor and rigidity
FTD	5-10%	Damage to frontal and temporal lobes	Personality changes, mood changes, disinhibition, language difficulties

Table 5: Characteristic and proportion of dementia subtypes [World Alzheimer Report 2009]

Another way of classifying dementia is by the brain area affected. When the cortical brain cortex is impaired, symptoms arise such as problems in memory, language, thinking and social behavior. Alzheimer's Disease is one example of cortical dementia. Disorders in the subcortical part of thebrain (layer under cortex) influence memory, emotion and movement [MUMENTHALER and MATTLE 2002].

2.4.1. Alzheimer's Disease

Alzheimer Disease (AD) is the most common disorder that causes dementia. First described in 1906 by a German doctor Alois Alzheimer, early symptoms of this disease include memory impairment, followed by disturbance in language and recognition skills, and motor and sensory symptoms which eventually appear in the later stages. Neuropsychiatric symptoms such as aggression, agitation, depression, apathy and hallucinations may occur during disease progression. These behavioral symptoms are classified into 3 groups: affective syndrome, psychotic syndrome and other neuropsychiatric disturbances. This classification should help physicians in diagnosing and providing better treatment for people with AD [LYKETSOS et al 2001].

AD differentiation includes a senile and pre-senile form. In the pre-senile subtype, the onset of dementia is below the age of 65, half of this subtype has a genetic predisposition to AD, it is also known as early onset familial AD (eFAD). In late onset or sporadic AD, symptoms appear after the age of 65. DSM-IV also divide AD types into subtypes with and without behavioral disturbance.

On average, patients live 6 years after being diagnosed with AD [KAY et al 2000]. Although survival rate is also correlates with the age when AD is diagnosed, persons diagnosed with AD at age 65 have approximately 8,3 years to live, meanwhile those diagnosed at 90 only 3,4 years [BROOKMEYER et al 2002]. However, AD is not main cause of death. Losing their ability to swallow, AD patients often die because of aspiration pneumonia or other infections [FORSTL et al 2005].

The hallmark of AD is neuropathological changes in the brain known as amyloid plaques[12] and neurofibrillary tangles[13], although other pathological alterations such as neuropil threads, granulovacuolar degeneration, and amyloid angiopathy may also be presented.

Amyloid senile plaques

Amyloid plaques accumulate between neurons, contain beta amyloid peptides (Aß) and fibrils, which are formed due to subsequent cleavage of amyloid precursor protein (APP) by ß- and γ- secretase [SWARTZ 1999] (Illustration 1). APP is an integral membrane protein, whose functions are still unknown, but it is suspected to play a role in synapses formation and plasticity.

APP is cleavaged by α- , ß- and γ- secretase through either amyloidogenic or non-amyloidogenic pathways. In non-amyloidogenic pathway, α-secretase split APP within Aß domain, forming sAPPα and C83. The cleavage in the middle of Aß domain is believed to have a protective property, preventing its deposition and aggregation [YAN and WANG 2007]. Alternatively via the amyloidogenic pathway, ß- secretase derived sAPPß and C99 from APP. C99 will be processed further by γ- secretase, generating 40 and 42 amino acids moieties [Aβ (1-40) and Aβ (1-42)]. [FRYER and HOLTZMANN 2005]

Although Aß$_{40}$ is the most common[14] form in human plasma and cerebrospinal fluid, Aß$_{42}$ is the predominant form of amyloid plaques and tends to aggregate more rapidly than Aß$_{40}$ in vitro. Aß$_{42}$ aggregation is suggested to play an important role in the initiation of plaque formation.

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12 Amyloid plaques are clumps of protein, are found in the extracellular tissue between nerve cells.
13 Neurofibrillary tangles are twisted filaments within neurons (intracellular).
14 Aß40 make out around 90% of all amyloid peptide produced by APP, while Aß42 only 10%.

The ratio between Aß$_{40}$ to Aß$_{42}$ seems to determine toxicity and pathological distribution of AD. At equimolar ratio (Aß$_{40}$ to Aß$_{42}$: 0,5-1) , Aß$_{40}$ may inhibit the formation of fibril by Aß$_{42}$ in vivo [KIM 2007]. This effect, may be due to the competition of monomeric Aß$_{40}$ and Aß$_{42}$ for binding to the ends of fibrillar amyloid aggregates [JAN et al 2008].
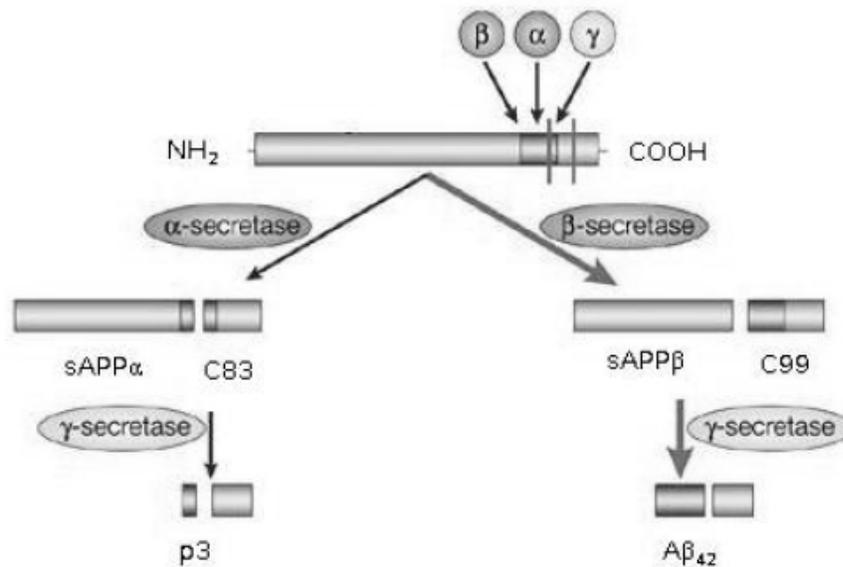
Illustration 1: Proteolytic processing of amyloid precursor protein (APP)

Accumulation of the beta amyloid peptide in senile plaques triggers some physiological changes in brain that may lead to cognitive deterioration (Illustration 2). Aß aggregation may cause disturbance in membrane integrity, causing depolarization of ion channel, alteration of ion homeostasis and dysregulation of signal transduction, leading to apoptosis [ARISPE et al 1993]. Oxidative stress, perturbation of intracellular calcium homeostasis, and inflammation may also be involved in this process [MATTSON et al 1993] [WYSS-CORAY and MUCKE 2002].
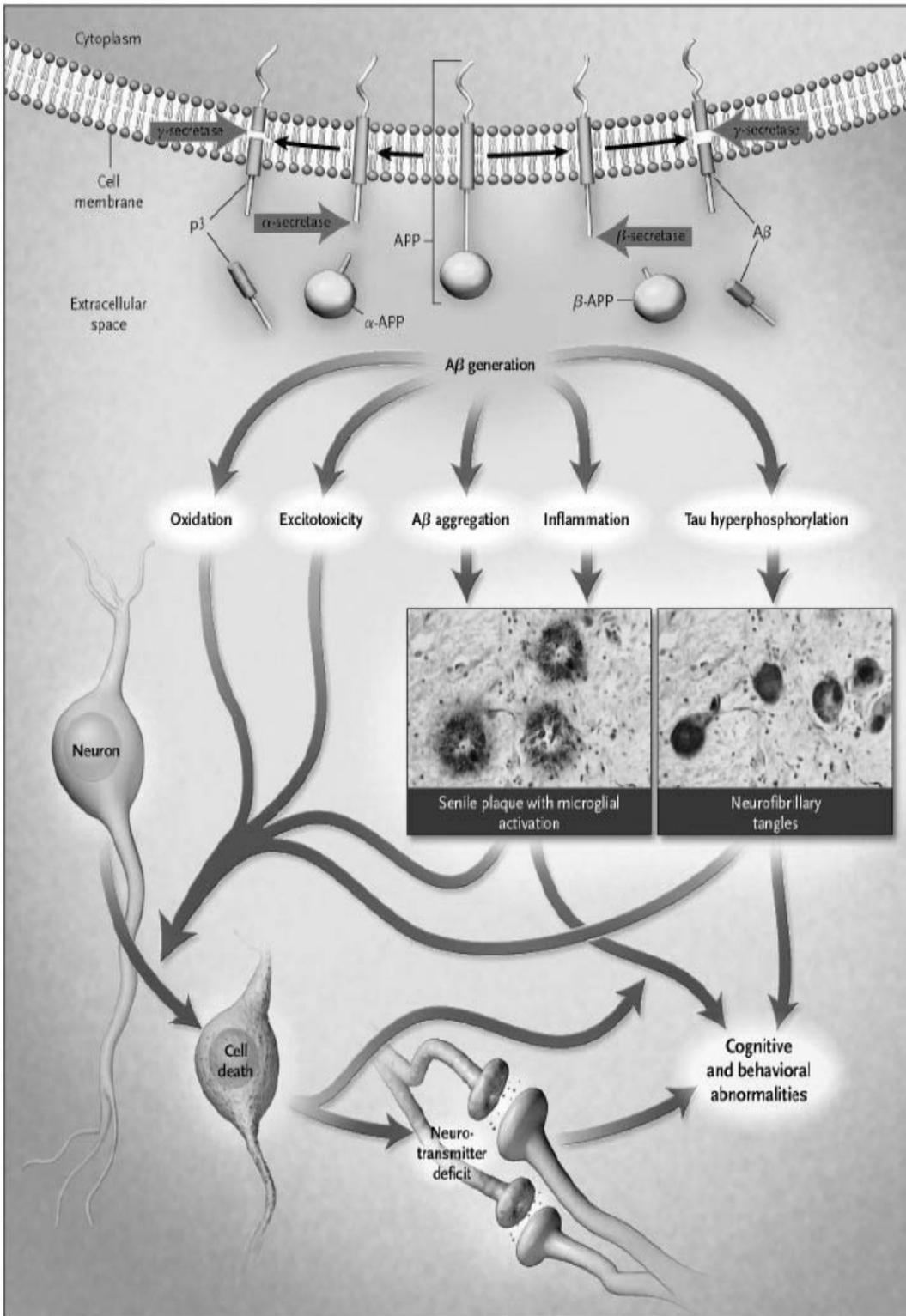
Illustration 2: Amyloid cascade [CUMMINGS 2004]

Since it is generally thought, that accumulation of Aß is responsible for the neurodegeneration in AD, researchers are trying to develop medication by finding an agent either to stop or inhibit Aß production. One approach is to make a vaccine that makes the immune system prevent accumulation of amyloid plaques or destroy them. After successful preliminary studies in mice, a clinical trial with vaccine AN-1792 failed and caused brain inflammation described as meningoencephalitis in humans [CHECK 2002]. Autopsy showed clearance of Aß from the AD brain, but numerous neurofibrillary tangles and neuropil threads lesions were unaffected, and severe dementia symptoms remained [NICOLI et al 2003]. Thus, although accumulation of amyloid plaques are significant in the development of AD, increasing evidence shows that beta amyloid is not the exclusive cause of cognitive deterioration [CARTER and LIPPA 2001].

Neurofibrillary tangles

Neurofibrillary tangles (NFTs) occur within cells, they consist of tau[15] protein, which is hyperphosphorylated and therefore tangles form insoluble aggregates called paired helical filaments (PHF). This aggregation result in loss of tau main function in stabilizing microtubules, causing disturbance in microtubule-dependent axonal transport and cognitive decline [VANDEBROEK et al 2006].

Phosphorylation of tau is regulated by the enzymes kinases and phosphatases. Some of the kinases, such as glycogen synthase kinase 3ß (GSK3ß) , phosphatidyl inositol 3-kinase (PI3K), and mitogen-activated protein (MAP) kinase, are activated by the increased Aß status and thus may play a role in tau hyperphosphorylation [FERREIRA et al 1997]. Protein phosphatase-2A (PP2A) on the other hand, has a function in regulating tau dephosphorylation [WANG et al 2007]. It is hypothesized that a decrease in PP2A activity is crucial for the

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15 Tau is a microtubuli-associated protein.

increased level of tau phosphorylation, rather than an increase in kinase activity [PLANEL et al 2001]. Regulation of PP2A is influenced by methylation reaction, thus it is postulated that there may be a link between tau phosphorylation, S-adenosylmethionine and homocysteine status in plasma [VAFAI and STOCK 2002].

Density of tangles is correlated with diseases duration and severity of cognitive loss [SPIRES and HYMAN 2005]. Neurofibrillary tangles are also abundant in FTD and other so-called tauopathies [LEE et al 2001].

A recent study suggests that Aβ toxicity may depends on tau-protein concentration [ROBERSON et al 2007]. In mice, decreasing tau-protein without changing the Aß level, results in behavioral improvement, postulating that tau is required for Aß toxicity [RAPOPORT et al 2002].

In addition, neurochemical change is also present in AD brain. The level of acetylcholin, a neurotransmitter involved in memory processing and learning, is decreased in the AD brain, where its decline is more evident in the advanced stages [DAVIS et al 1999].   Loss of cholinergic neurons[16] due to a decline in cholinergic activity of the cholinergic synthetic enzyme ChAT (Cholin Acetyltransferase) is associated with memory impairment in AD[17] [PAPPAS et al 2000]. Glutamate activity is also decreased, excitotoxicity[18] of glutamate mediated by N-methyl-D-aspartate (NMDA) receptors could lead to neuron death [GROSSBERG and KAMAT 2009].

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16 Cholinergic neurons are neurons that utilize acetylcholin.
17 Two enzymes involved in Acetylcholin regulation are synthesizing enzyme Cholin Acetyltransferase (ChAT) and catabolic Cholinesterase .
18 Excitotoxicity means over-stimulation to its membrane receptor.
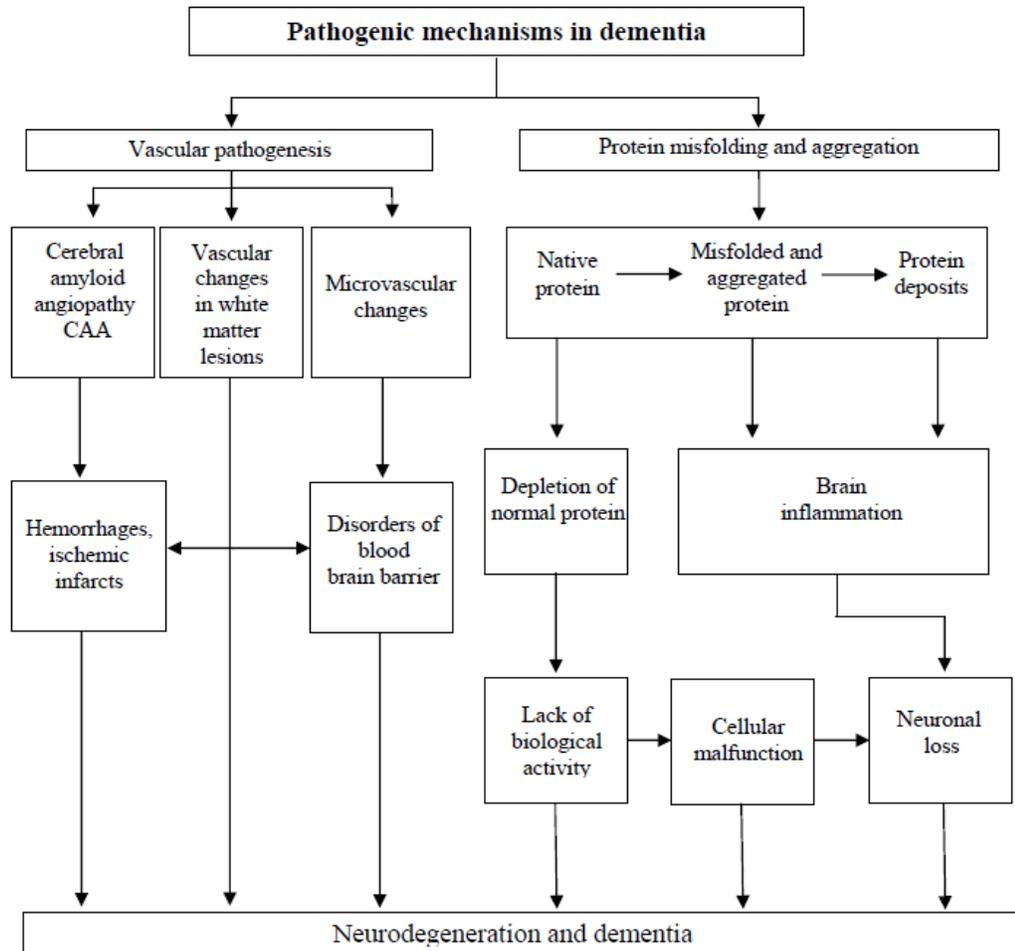
Illustration 3: Pathophysiology of dementia [KASOHA 2010]

2.4.2. Vascular Dementia

Vascular dementia (VaD) is dementia caused by cerebrovascular disease. Unlike AD, memory impairment might not become prominent in the early stages and cortical dementia symptoms such as apraxia and aphasia might not be present. A connection between CVD and dementia is difficult to judge on symptoms alone, since infarcts may be small or localized in subcortical regions [KRAMER and WETZEL 2009].

Furthermore, the heterogenity of cerebrovascular disorders make it difficult to diagnose. Neuron death in VaD caused by stroke could result from ischemia[19] or hemorrhages[20].

To date, although there are some clinical diagnostic criteria for vascular dementia[21], most of them diagnose vascular dementia based upon symptoms of AD imposed with vascular events. Differences between each clinical criterion include varied definitions of cognitive decline, vascular cause, onset and disease progression, and subtypes of vascular dementia. These many standards may cause confusion in research and clinical practice, thus may affect disease recognition and treatment [WIEDERKEHR et al 2008]. An international consensus for diagnosing vascular dementia is urgently needed.

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19 Ishemia is condition of restricted blood flow, disturbing blood transport to cells.
20 Hemorrhage means bleeding, caused by ruptured blood vessel or arteriovenous malformation.
21 Reviewed by Wiederkehr et al (2006) are DSM-IV, ICD-10, Hachinski Ischemic Scale (HIS), Ischemic Scale of Rosen, California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC), and National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN).

Cerebrovascular events	Disorder	Pathological Cause	Features
Hemorrhage	Non traumatic subarachnoid hemorrhage	Ruptured cerebral aneurysm Arteriovenous malfomation	- high morbidity rate - significant cognitive deficiency - memory impairment - deficit in executive functions
	Cerebral Amyloid Angiopathy (CAA)	Aß accumulation in cerebral blood vessels[22]	
Ischemia	Subcortical atherosclerotic encephalopathy (Binnswanger's Disease)	Extensive demyelination and destruction of subcortical White Matter (WMLs)	- apathy - lack of drive - mild depression - alterations of mood - slow information processing
	Strategic infarcts	Infarction of thalamus, frontal white matter, basal ganglia; disconnect neuron systems	- memory impairment - depend on localization of infarcts
	Large vessel disease[23] or Multi Infarcts Dementia		- sudden onset - stepwise progression - not often combined with AD compared to other ischemic dementia - neurological symptoms vary, depend on size and localization of lesions - aphasia, apraxia and agnosia - inattention syndromes
	Small vessel disease or Subcortical Ischemic Vascular Dementia (SIVD)	Lacunar infarct[24], also known as lacunar state dementia	- associated with age and hypertention
		Cerebral Autosomal Dominan Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)	- genetic disorder, mutation of chromosome 19 - cognitive decline at early age

Table 6: Cerebrovascular events that cause dementia symptoms. [KRAMER and WETZEL 2009]

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22 ACC is common in AD patients, and could make cerebral blood vessels more prone to rupture
23 Large vessel disease or MID refers to occlusion of main branch of cerebral arteries, caused by atherosclerotic plaques or emboli from cardial origin
24 Lacune is cavity filled with Cerebrospinal Fluid (CSF) in basal ganglia or white matter.

VaD is essentially preventable, since onset of dementia happens *after* a cerebrovascular event. Therefore, recent studies propose the use of a broader term to include mild cognitive loss before dementia, namely Vascular Cognitive Impairment (VCI). The definition of VCI covers all cognitive burden resulting from cerebrovascular disease, and some VCI may develop into incurable dementia. [ERKIJUNTTI and GAUTHIER 2009].

2.4.3. Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD)

Lewy bodies are abnormal protein structures in the brain, consisting of α-sycnuclein and ubiquitin protein, normally found in brain stem and cerebral cortex. Clinical symptoms and pathological findings of DLB often overlap with AD and PDD [BYRNE 1997]. At autopsy, most DLB patients also have neuritic plaques and neurofibrillary tangles and memory loss may be profound in the early stage, leading to false diagnosis. Indeed, difficulties in distinguishing LBD and AD in its early phase, has lead to the development of a new term, the Lewy Body Variant of Alzheimer's Disease (LBV) [HANSEN et al 1990].

The clinical features of DLB are fluctuations in cognitive performance, visual hallucinations and systematized delusions and spontaneous parkinsonism, thus psychiatric symptoms are usually more prominent than cognitive. Compared to AD, DLB patients seem to show greater deficits of attention, psychomotor speed and visuospatial ability [HANSEN et al 1990].

Lewy bodies are also found in Parkinson's patients, with or without dementia symptoms. While in DLB, Lewy bodies are found predominantly in the cortical area, in PDD they are found in subcortical [LENNOX and LOWE 1996]. In addition, decline of dopamine activity due to neuron degeneration in substantia nigra may explain motoric symptoms typical to PD, such as bradykinesia[25], rigidity but no loss of muscle strength, tremor, and postural instability.

About 40% of PD patients developed dementia with cognitive, mood and behavior disturbance in later stage and prevalence may increased with disease duration [EMRE 2008].

2.4.4. Alcohol related dementia

Clinically, dementia from chronic alcohol abuse could be caused by direct neurotoxicity effect of alcohol, known as primary alcohol dementia, or due to chronic thiamine malabsorption and deficiency, which leads to Wernicke-Korsakoff syndrome (WKS).

In primary alcohol dementia, there exist some biochemical changes in the brain, such as NMDA receptor hyperexcitability and hyperhomocysteinemia, although its relationship to brain disorder is still uncertain. Cases of this disorder are rare and probably still could be cured with appropriate treatment such as thiamine supplementation and alcohol abstinence [MORIYAMA et al 2006].

Wernicke's encephalopathy is an acute neurological disorders, characterized by oculomotor abnormalities, cerebellar dysfunction, and altered mental state or memory impairment, usually followed by Korsakoff's syndrome, which appears as

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25 Bradykinesia is slowed ability to start and continue movements.

profound amnesia, disorientation and frequent confabulation. Jeusen and Pakkenberg (1993) have suggested, that neurotoxic features of alcohol may cause a disconnection syndrome between neurons, preventing nerve pathways from being activated. Another theory by Pfefferbaum et al (2004) hypothesized a combination of liver dysfunction, poor nutrition and chronic exposure to alcohol, to cause brain damage [PFEFFERBAUM et al 2004].

The exact mechanism of this syndrome is still unclear at present. Scientists suspect, there may exist a genetic predisposition to thiamine deficiency caused by chronic alcohol abuse. This could explain why some people tend to develop WKS, but further researches are still needed to confirm this. It should be noted that Wernicke-Korsakoff syndrome is partially reversible [DOWEIKO 2001].

2.4.5. HIV Dementia

Dementia due to HIV is widely known as AIDS Dementia Complex (ADC). The death of nerve cells in the brain in this disorder is caused by neurotoxins produced by the HIV-virus. These toxins, such as TNF-alpha, cytokines, interleukins, chemokines, nitric oxide, and excitatory amino acids, induce inflammation in the surrounding environment [BRABERS and NOTTET 2006]. HAART (highly active antiretroviral therapy) medication seems to increase the average life span of AIDS patients with dementia, from 6 months without treatment to 38 months with a regular regimen [MC ARTHUR 2004].

2.5. Risk Factors and Preventions

The development of dementia, so some scholars believe, takes place over a long period of time before first symptoms appear. During this process, some factors may accelerate or delay the onset of disease. Old age seems to be the significant risk factor for dementia. Epidemiological studies show, that the risk of developing dementia rises with advancing age.

Risk factors for dementia may be different for each gender [ARTERO et al 2008]. Many scientists believe, women are more at risk because of the decline of estrogen after the menopause. Moreover, women live longer than men and are more prone to diabetes, another risk associated with dementia.

Risk factors such as depression, becoming emotionally dependent on others, and becoming socially isolated has more damage on women, where for men, physical health such as diabetes and stroke increase more chance of developing dementia. Researchers believe, the development of neurodegenerative diseases are multifactorial and not caused by a sole risk factor, but from interactions between genetic susceptibility and environmental exposures [GREENAMYRE et al 2003].

Swedish Council on Technology Assessment in Health Care (SBU) in its review "Dementia - Epidemiology and Etiology" in 2008 suggested some hypotheses as risk and protective factors, summarized from studies between 1985 to 2004.

Hypothesis	
Genetic	Familial aggregation ApoE Ɛ4 allele
Vascular	Smoking Alcohol consumption Blood pressure Diabetes Mellitus Cholesterol/Obesity Cardiovascular diseases/Atherosclerosis Homocysteine Anti-hypertensive statins Hormonal Therapy
Inflammatory	NSAIDs (Non-steroidal Anti-Inflammatory Drug) Inflammation markers
Toxic	Head trauma Aluminum Occupational exposure
Oxidative	Diet : Folate / Cobalamine deficiencies
Psychosocial	Depression Low education Socioeconomic status Leisure activities Social network Personality

Table 7: Risk factors of dementia [SBU 2008]

2.5.1. Genetic hypothesis

Suspicion that dementia may be due to genetic defects, is derived from studies of Down's Syndrome. About half the people with Down's Syndrome develop AD after they reach the age of 35 [SCHALLENBERG et al 1992]. The hallmark of Down's Syndrome is an extra copy of chromosome 21 in each cell; as a result, the genes that cause AD have 3 copies instead of 2. The mutation of amyloid-beta precursor protein (APP) gene in chromosome 21 may cause the excess production of beta

amyloid peptide in cells therefore account for the increased risk. Moreover, presenilin1 (PSEN1) and presenilin (PSEN2) genes, which are located in chromosome 14 and 1 respectively, are also suspected to cause Familial AD with early onset dementia. Presenilin mutations are linked to γ-secretase activity [SCHEUNER et al 1996]. The mutation in PSEN1 may increase the proportion of C99 peptide that is cleaved by γ-secretase, therefore causing an increased production of $Aß_{42}$ [SMALL et al 2010].

For late onset of the condition, which is more common, the ApoE Ɛ4 gene on chromosome 19 is taken into account [BOOKHEIMER et al 2000]. There is further evidence concerning an increase of the involvement of chromosome 10, 12 and 3 to late onset AD [BERTRAM et al 2000].

Genetic factors may also play a role in the development of Parkinson's disease . Mutation in gene coding for α-synuclein protein, parkin and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) are known to be associated with protein misfolding and aggregation in PD [GREENAMYRE et al 2003].

Dementia that develops purely from gene mutations is very rare, it accounts for only less than 1% of all cases of dementia. Even people with this genetics disposition have only an *increased risk* of developing dementia, and not all cases develop into disease itself. Approximately half of AD's patients carry none of above mentioned genes, which leaves other unknown genetic factors, or environmental interactions that respond to genetic disposition to determine onset.

2.5.2. Vascular hypothesis

Risk factors for cardiovascular disease, such as hypertension, high cholesterol level, obesity, high homocysteine plasma levels, also smoking, alcohol consumption, and obesity may increase the risk of atherosclerosis, and hence reduce blood supply to brain, resulting in stroke and other brain damage. In the matter of VaD and diabetes type 2, lower cognitive function is found in persons with high HbA1c[26]. [CUKLERMAN-YAFFE et al 2009]

Vascular pathology of dementia involved inflammation of blood vessels, vascular fibrosis and structural changes such as denervated cortical microvessel. Impairment of perivascular cholinergic nerve terminals from the basal forebrain may cause deregulation of cortical cerebral blood flow (CBF). The brain need a constant blood supply, since it has no reserve of glucose and oxygen, reduced blood flow (perfusion) to the brain may disturb neuronal function [HAMEL et al 2008].

Most scholars agree that lowering homocysteine, cholesterol levels and blood pressure is important to prevent vascular dementia. Exercise, controlling inflammation and nonsteroidal anti-inflammatory drugs are also considered beneficial.

2.5.3. Inflammatory hypothesis

High concentration of inflammation markers such as cytokine, C-reactive protein (CRP) and activated complement cascade protein, are found in senile plaques and neurofibrillary tangle in the brains of people with AD [McGEER and McGEER

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26 Average blood sugar control over 6-12 weeks period, normal rate 6%

2004], suggesting a possible involvement of inflammatory process in the development of AD. Beta amyloid deposition and neurofibrillary tangles may act as irritants, stimulating a chronic inflammation that leads to neuron degeneration and synaptic changes. Further, signals emanate from injured neurons and imbalances between pro- and antiinflammatory process may also trigger inflammation response in the brain [WYSS-CORAY and MUCKE 2002].

Interaction between beta amyloid (Aß) and cells involved in the inflammatory process such as the microglia[27] and the astrocytes are thoroughly investigated in recent years. The clustering of migroglia around beta amyloid deposits may be an attempt to clear beta amyloid through phagocytosis [KOPEC and CARROLL 1998]. Some reports indicate that the degradation mechanisms of phagocytosed Aß fibrils may be overloaded or even impaired, causing the undegraded Aß remnants remain stored within microglia for a long time [ARD et al 1996]. Moreover, Aß can induce expression of nitric oxid synthase (NOS) in microglia and thus resulting the loss of neurons. This finding suggests that neuronal damage may result from products released by activated microglia rather than direct action of beta amyloid [WELDON et al 1998]. Microglia may also produced reactive oxygen species, which exacerbate neuron damage through oxidative stress [TUPPO et al 2005].

Since inflammatory factors such as microglia, astrocytes, cytokines and complement factors have multiple functions, their role in the development of neurodegenerative diseases is unclear [WYSS-CORAY and MUCKE 2002]. The debate, whether inflammation process has beneficial or detrimental effect, lead to discussion to what extent inhibiting inflammation can reduce neuron degeneration.

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27 Microglia are the immunologically competent cells whose functions include chemotaxis, phagocytosis and secresion of a variety of cytokines and proteases, they are the resident macrophage of the central nervous system [KOPEC and CARROLL 1998]

Long-term NSAID (Non-Steroidal Anti-Inflammatory Drugs) use are proved to have a preventive effect on dementia, particularly ibuprofen [VLAD et al 2008]. This effect may be due to partial clearance of beta amyloid in the brain, since certain NSAIDs have inhibitory effect on Aß production [WEGGEN et al 2001]. However one cohort study in 2009 [BREITNER et al 2009] and one randomized double blind trial [ADAPT Research Group 2008] showed that drugs such as naproxen and celecoxib did not delayed the onset of dementia and naproxen even seemed to have a detrimental effect[28]. This contradiction may be related to immunologic diversity of person with AD; the outcome of inflammatory responses depends on the specific trigger and on the genetic background on which it occurs [WYSS-CORAY and MUCKE 2002].

2.5.4. Oxidative hypothesis and nutrient deficiencies

Oxidative stress[29] has been identified to play an important role in the pathogenesis of Alzheimer's disease. Age-related accumulation of reactive oxygen species (ROS) may result in cellular damage and neurons seem to be vulnerable to free radicals attack for various of reasons. Reactive oxygen species (ROS), including superoxide, hydroxyl radicals, hydrogen peroxide and nitric oxide, are normal byproducts of oxidative phosphorylation and various tissue oxidases. Some events may trigger the overproduction of ROS and thus impair antioxidant defense system [BEHL and MOOSMAN 2002]. Factors such as microvasculature changes, increase in oxidized proteins and lipids, alterations in membrane micro-environment and structure, as well as alteration in calcium buffering ability and an increase vulnerability of neurotransmitter receptors to oxidative stress, may

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28 ADAPT trial had to be stopped early, due to possible negative side effect of two painkillers ; naproxen and celecoxib.

29 Oxidative stress is defined as imbalance between the production of reactive oxygen species (ROS) and the defense antioxidant mechanism for removing ROS.

facilitate the formation of ROS [JOSEPH et al 2005].

Compared to other organs, the human brain is believed to have relatively reduced capacity for cellular regeneration. A high proportion of easily oxidizable polyunsaturated fatty acids in neuron's membrane and its high rate of oxygen utilization make neuron prone to oxidation process [CHRISTEN 2000]. Moreover, redox-active transition metal ions are abundantly present and there are also a critical decline in endogenous antioxidant production [JOSEPH et al 2005] [BUTTERFIELD et al 2002]. In the brain, oxidative stress manifested as lipid peroxidation, protein oxidation, DNA oxidation and mitochondrial abnormalities, they all are related with free radicals formation in its process [ZANA et al 2007].

These oxidative events seem to be target specific. The nitration of tyrosine[30] within the α-synuclein protein is found to accumulate in the Lewy bodies in Parkinson Disease, and within the tau protein in Alzheimer's disease. Moreover, the affected brain regions showed a reduced activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GSHPx) and glutathione reductase (GSHRd) [ANDERSEN 2004].

The ability of cells to counteract oxidative stress seems to decline with age, this may contribute to beta amyloid protein buildup in the brain of elderly with Alzheimer's disease [ANDERSEN 2004]. Increased oxidation of mitochondrial DNA, protein oxidation and lipid peroxidation have been observed in the elderly brain, with and without AD, but they seem to be more marked in the AD brain. End products of lipid peroxidation,such as malondialdehyd, peroxynitrite, carbonyls, advanced glycosylation end products, superoxide dismutase-1 and heme oxygenase -1 , are found within the AD brain, especially in neurofibrillary tangles [CHRISTEN 2000].

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30 Protein nitration is a marker of protein oxidation.

In animal experiment, the increased deposition of beta amyloid induces production of superoxide, which then in turn may triggers the synthesis of other oxygen species, the sequestration[31] of nitric oxide (NO), and impairment of membrane calcium pumps and enhancement of calcium influx through glutamate receptor [MATTSON and CHAN 2003].

But recently, evidence suggests that the formation beta amyloid and neurofibrillatory tangles may be parts of the protective response against oxidative stress [MAMELAK 2007] [PERRY et al 2002]. At physiological concentrations, beta amyloid has been shown to have a neuroprotective and antioxidant properties, thus beta amyloid generation is postulated to be aimed to reduce oxidative stress, prevent apoptosis, and promote tissue degeneration [MAMELAK 2007] [ROTTKAMP et al 2001]. This may explain, why beta amyloid is not toxic as a whole substance. Aggregated amyloid species is produced when energy shortage and calcium dysregulation alters amyloid metabolism [ROTTKAMP et al 2001].

The role of oxidative stress in the pathology of dementia is still a matter of debate. It may act either as the primary initiation event of neuronal injury or as the intermediate event that potentiate the cell damage. Recent studies conclude some events leading to the generation of reactive oxygen species and their interactions (Illustration 4). Beta amyloid accumulation, glial inflammation and mitochondrial dysfunction are associated with the production of free radicals [ANDERSEN 2004].

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31 Sequestration of nitric oxide molecules may impair NO-dependent dilatations.
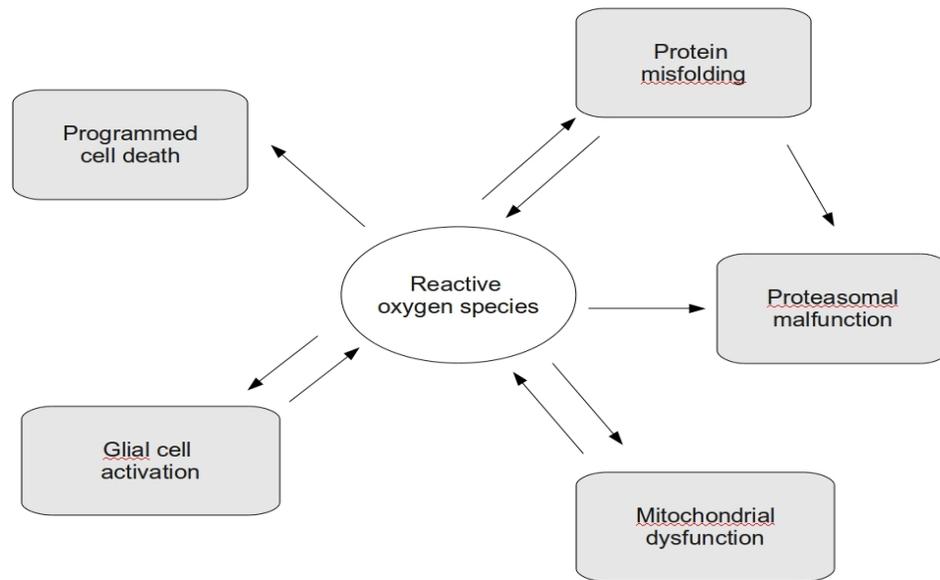
Illustration 4: ROS production in the cycle of events leading to neurodegeneration [ANDERSEN 2004]

Considering oxidative stress as an important event in neuron degeneration, reducing brain vulnerability to oxidative stress or inhibition of this reaction may serve as an effective approach in prevention and therapy of dementia. Indeed, the oxidative stress induced by beta amyloid can be completely abrogated in mice experiment with antioxidant therapy [HAMEL et al 2008].

Nutrition may be utilized as source of antioxidants, supplementation of vitamin E in combination with vitamin C at high dose, may be beneficial to prevent neurodegeneration [ZANDI et al 2004]. The protective effect of antioxidant vitamins and its limitations have been investigated in various studies and will be discussed later in the next chapter.

Other condition, that may induce oxidative stress in the brain is hyper-

homocysteinemia. In animal experiment and human culture brain cells, homocysteine is toxic to neuronal cells and potentiate the effect of beta amyloid, as they both induce calcium influx and oxidative stress leading to cell's apoptosis [PEI et al 2001]. Moreover, homocysteine is reported to modulate copper toxicity, by enhancing the generation of hydrogen peroxide [WHITE et al 2001],

Elevated level of plasma homocysteine is usually accompanied by low folate and cobalamine level, since they are all involved in one-carbon metabolism[32]. The folate metabolism may provide an epigenetic link between nutritional intake and the development of neurodegenerative illnesses. Deficiencies of folate and cobalamine intake with food, but also gene polymorphisms in enzymes regulating homocysteine may increase plasma homocysteine level, thus disturbing the production of S-adenosyl methionin (SAM), an important methylating agent for various functions in cell. In vitro, disturbance in homocysteine metabolism increases the production of S-adenosylhomocysteine (SAH) and results in reduced methylation of protein phosphatase 2A (PP2A), by inhibiting PP2A methyltransferase (PPMT). Reduced PP2A methylation is associated with the accumulation of phosphorylated tau. On the other hand, incubation of neuron with SAM enhance PP2A methylation, thus resulting neuroprotective effect [SONTAG et al 2007].

Membrane lipid peroxidation may have a role in the impairment of glucose transport by beta amyloid peptide. The product of lipid peroxidation, 4-hydroxynonenal, tends to conjugate with the neuronal glucose transport protein GLUT 3, thus impairs glucose uptake into the cells. When glucose uptake is compromised, cellular ATP level decreases, preceding neuron degeneration [MARK et al 1997].

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32 More about one-carbon metabolism and methylation process in chapter 3.

2.5.5. Toxin hypothesis

Dementia symptoms can be shown by kidney failure patients, who are exposed to aluminum through dialysis machines. It is then postulated that higher aluminum consumption, for example through drinking water, may increase the risk of cognitive decline. People with kidney failure are most vulnerable, since aluminum elimination is less than people with healthy kidneys, and thus may accumulate in the body. Recent studies have shown there is insufficient evidence to cite aluminum as the direct cause of dementia, since concentration of aluminum in the AD brain is little or absence [LANDSBERG et al 1992].

On the contrary, the level of zinc is significantly increased in an AD-affected cortex [RELIGA et al 2006]. Redox reactive metals such as copper and iron are also believed to play a role in neurodegeneration. They are reported to accumulate in the brain of people with AD and may promote generation of reactive oxygen species by amyloid peptide [WHITE et al 2001].

Environmental toxins seem to play an important role in the development of Parkinson's disease (PD). Occupational exposure to manganese and some pesticides such as rotanone and paraquat are suspected to trigger the neurodegeneration of brain cells by causing mitochondrial dysfunction [GREENAMYRE et al 2003].

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is another chemical substance known to cause symptom of Parkinson's disorder. MPTP is a protoxin that can cross blood brain barrier and is metabolized to form 1-methyl-4-phenylpyridinium (MPP$^+$) ion. MPP$^+$ is then actively transported into dopamine neurons, where it inhibits respirations at the level of complex I in mitochondria [GREENAMYRE et al 2003].

In experiments with rats, insecticide rotenone causes the death of dopaminergic neurons in substantia nigra and thereby inducing parkinsonian syndromes. Like MPP^+ ion, rotanone inhibits complex I enzyme in electron transport chain, resulting systemic mitochondrial dysfunction [BETARBET et al 2006]. Complex I inhibition is uniformly happened throughout the brain and the rest of the body, but dopamine neurons of substantia nigra are particularly sensitive to this defect [GREENAMYRE et al 2003].

Data from epidemiological studies have constantly shown, that pesticide exposure is associated with Parkinson's disease in dose and time-dependent manner [BROWN et al 2006] [HANCOCK et al 2008] [ELBAZ et al 2009]. A significant positive association was observed if the pesticides being used for long period (>10years) or in a large dose [BROWN et al 2006]. At current knowledge, there are enough evidences to associate a long-term pesticide exposure to Parkinson's disease, but insufficient for causal relationship [BROWN et al 2006].

2.5.6. Psychosocial hypothesis

A higher level of education has been thought to act as a protective factor against dementia. Indeed, according to some studies, people with higher education have delayed the onset of disease, but deterioration of cognitive function after onset is more rapid than people with less education [HALL et al 2007]. Furthermore, Snowdon et al (2000) have found an association between writing style and the occurrence of AD. Low linguistic ability in early life may lead to a higher risk of susceptibility of developing AD in old age [SNOWDON et al 2000].

Another psychological factor could be depression, elderly people with a depressed

mood have more risk of developing Alzheimer Dementia [DEVANAND et al 1996], but it still not clear whether depression is a risk factor or an early sign of changes in brain. Inflammation of brain tissue during depression might play a role in the onset of dementia [SACZYNKSI et al 2010].

Socioeconomic conditions such as poverty, affect the risk of developing dementia indirectly, since it could be responsible for poor nutrition in childhood as well as limited educational opportunities both of which may be instrumental in the development of dementia in later life.

Physical activity is regarded as a protective factor against dementia, although some studies have been unable to demonstrate a direct link between exercise and dementia, one benefit would be a reduction in the risk of cardiovascular diseases. People who exercise tend to be more socially active, which can enhance cognitive function, which is beneficial in terms of prevention as well as therapy treatments [HEYN et al 2004]. Furthermore, activities that have mental, physical or social components might have a preventive effect on dementia [FRATIGLIONI 2004].

2.6. Diagnosis

Early diagnosis of dementia is very desirable ; it may decelerate the progression of the illness, through medication and planning for future since the patients are still able to make decisions for themselves. The patient's history, physical examination, laboratory test and psychiatric evaluation are crucial to differentiate dementia from other dementia-like conditions.

In practice, neuropsychiatric symptoms are identified using screening instruments. Test like MMSE[33], MOCA[34], clock drawing test, TFDD Test[35] , DemTec[36] could measure memory, language, orientation, visuospatial skills, concentration, and executive functioning. Some tests may have limitations in sensitivity and the ability to determine the severity of symptoms thus a combination of multiple tests is advised.

There is a range of electronic diagnostic imaging tools available now, such as Magnetic Resonance Imaging, Single-photon Emission Computed Tomography, Positron Emission Tomography and Computed Tomography, which provide visualization on structural or physical changes in brain neurons, thus identifying the severity of disease. EEG[37] may help to differentiate brain disorder from delirium or depression, as the AD brain has slow wave.

Measuring the concentration of beta amyloid, total tau and hyperphosphorylated tau in cerebrospinal fluid may give a clue about initial damage to brain neurons and therefore allow the early detection of dementia. Although acquiring these biomarkers requires invasive and uncomfortable procedures, this method has high sensitivity and selectivity.

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33 Mini-Mental State Examination
34 Montreal cognitive assessment
35 TFDD is german abbreviation , it stands for "Test zur Früherkennung von Demenz mit Depressionabgrenzung", early identification of dementia in dissociation from depression
36 DemTec is Dementia Detection Test
37 Electroencephalography is an instrument to measure brain wave activity.

2.7. Therapy and treatment

Medication

Since dementia cannot be healed, medication could only therefore slow the progression of the disease. In people with AD, deficiencies in the brain cholinergic system and of other neurotransmitters[38] are present, thus drugs such as cholinesterase inhibitors[39] (donepezil, galantamine and rivastigmine) and glutamate regulator[40] (memantine) could help the improvement of cognitive symptoms. Serotonin reuptake inhibitors (SSRIs) may help lighten depression, a symptom that often occurs during the disease's progress.

Some studies suggest a supplement of high dose vitamin E might slow progression of Alzheimer's disease [SANO et al 1997], while others postulate that vitamin E may have an adverse effect and thus a higher risk of mortality [ISAAC et al 2008]. Neither hormonal treatment with estrogen nor use of anti-inflammatory agents can have a beneficial effect on symptoms of Alzheimer's dementia [SHUMAKER et al 2003].

Managing the vascular risk factor may also help decelerate the progression of VaD, statins to lower cholesterol level, maintaining blood pressure, blood sugar and the homocysteine level may prevent future strokes.

Antipsychotic medication dispensed to alleviate behavioral symptoms, such as anxiety, agitation, aggression and hallucinations, may have undesirable side effect namely an increased risk of death [WANG et al 2005] and therefore should be

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38 Other than acetylcholin and glutamate, norepinephrine, serotonin, somatostatin, and corticotrophin-releasing factors are also decline in AD brain.

39 Cholinesterase is a catabolic enzyme that breaks down acetylcholin to cholin and acetate group. Inhibiting this enzyme would result in an increased level of acetylcholin in brain. This drug is usually used in the early to moderate stage of AD.

40 In the case of AD, glutamate receptor (NMDA) is overactive. Memantine, which usually used in the moderate to severe stage of dementia, is NDA antagonist.

used with careful consideration. Pharmacological treatment of sleep disturbance should be applied only if other therapies have failed.

Psychosocial Therapies

The American Psychiatric Association (2007) Guidelines for Treatment of Patients with Alzheimer's Disease and other dementias classifies nonpharmacological interventions into 4 categories:

– behavior-oriented approaches
– emotion oriented (reminiscence therapy, validation therapy, supportive psychotherapy, sensory integration, and simulated-presence therapy)
– stimulation oriented (recreational activities, music or dance therapies, exercise, aromatherapy)
– cognition oriented (reality orientation, cognitive retraining, skills training)

Although researches into long-term efficacy of psychosocial therapies are limited, a positive effect of behavior might be observed on sensory stimulation or music therapies [GODDAER and ABRAHAM 1994].

3. Nutrients associated with central nervous system disturbance

Neurodegenerative diseases such as Alzheimer's or Parkinson's disease are not considered nutrition-related diseases. However, neurological and psychological symptoms have long been associated with nutrient imbalance[41]. Researches in the last decade seem to support the notion, that nutritional factors may be important to prevent neuron degeneration.

To date, it is still unclear of how nutrition may affect neuronal cell death. Neurons needs nutrients to assure their functions, namely to transmit and process electrical and chemical signals, a chronic severe nutrient deficiency or excess may present symptoms of brain disturbance.

Indeed, nutritional status of elderly with dementia is significantly different from healthy elderly. Low serum levels of vitamin B_{12}, vitamin E, vitamin C, folate as well as the condition of hyperhomocysteinaemia (which can be caused by B-group vitamin deficiencies) are observed in dementia patients in clinical studies and these factors have been associated with an increased risk of AD [SCHELTENS 2009].

Scientists are still unsure, if nutritional deficiency is one of the risk factors for developing dementia or one consequence from neuronal cell defect. Either way, evidences show that some nutrient-related metabolic pathways, such as oxidative stress, lipid peroxidation, mitochondrial dysfunction, glucose transport system and abnormal methylation process, may be involved in protein misfolding and aggregation, the hallmark of Alzheimer's disease. In cell cultures, these events can be affected with nutritional intervention. Studies have already showed promising results with antioxidants, ω-3 fatty acids and homocysteine-related vitamins. As a

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41 One of the classical symptoms of pellagra, a disease caused by the chronic deficiency of niacin, is dementia.

modifiable risk factor, nutrition may be able to play the key role in the prevention of cognitive decline.

Nutrition, cardiovascular diseases and neurodegenerative diseases

Considering the strong relationship between nutrition and cardiovascular diseases, even if nutrients do not affect neuron degeneration directly, they may influence the development of dementia through vascular-related risk factors. The case of vascular dementia show that integrity of vascular system is essential for the functioning of the brain [KALARIA 2010]. Based on this fact, the current dietary recommendations to prevent dementia are the same with those to maintain a healthy heart [MORRIS 2011]. Either from vascular or neurodegenerative mechanisms , or both, increasing evidence is supporting the relevance of nutrition in the prevention of dementia.

Nutrition and the brain's transport systems

On current knowledge, there are 2 pathways for nutrients to enter the brain, either from blood through blood-brain barrier or through the choroid plexus of the blood-cerebral spinal fluid barrier by mechanisms of facilitated diffusion, active transport, binding receptors and ion channels. To ensure the brain high rate of nutrient turnover, these complex transport systems and physiological mechanisms have homeostatic functions, which transport less into the brain when plasma levels are high and vice versa [MORRIS 2011].

Data show a connection between disturbances in nutrients transport and neurons degeneration. Such as the glucose transport systems, which facilitated glucose passage across neurons' membrane, the membrane transporter proteins GLUT 1 and GLUT 3 were found to be decreased in AD brain . This impairment in glucose

metabolism may lead to hyper-phosphorylation of tau protein by down-regulating the tau O-GlcNAcylation[42] [LIU et al 2008]. The same condition of the decreased GLUT 3 level also found at a bigger extent in the brain of diabetes type 2 patients, which may explain why diabetes is one risk factor for AD [LIU et al 2009].

The brain glucose utilization is only one example of how nutrient being processed in a long complex pathway before getting utilized in the brain. The process of nutrient breakdown, absorption, transportation and utilization depend on many enzymes, metabolites, and other components of cells that continuously interact with each other. That considered, nutrition can not be the sole cause nor solution for dementia related diseases. Interplay between genetic disposition with nutrient and environmental exposure, is postulated to be mediated by epigenetic[43] mechanism.

Epigenetic approach

Like many chronic diseases, the most common form of AD (late onset Alzheimer's disease) do not follow Mendelian hereditary rules of genetic. Environmental exposure, occurring at specific stage of development e.g. during gestation, may increase illness' susceptibility. Epigenetics is defined as the heritable, but reversible, regulation of various genomic functions that occur independently of the DNA sequence [SMITH and MILL 2010]. Changes in gene expression and cellular phenotype are caused by non-genetic factor, without changing DNA gene sequence. Environmental changes, such as exposure to toxins, stress and nutrients deprivation during important phase of life, may lead to epigenetic

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42 O-GlcNAcylation is a type of protein O-glycosylation by which the monosaccharide β-*N*-acetylglucosamine (GlcNAc) attaches to serine/threonine residues via an O-linked glycosidic bond [LIU et al 2004].

43 Epigenetics literally means "above genetics", the term is born from the understanding, that above the DNA sequence there is a second layer of information (the epigenome) that regulates genomic functions, including where and where genes are turned on or off [SMITH and MILL 2010].

modifications [IRAOLA-GUZMÁN et al 2011].

Epigenetic mechanisms that might affect the functioning of genes are e.g. nucleosome positioning, post-translational histone modifications, the action of small RNAs, and DNA methylation[44]. Altered in methylation has been proposed to explain the relationship between elevated level of plasma homocysteine and the development of neurodegenerative diseases [IRAOLA-GUZMÁN et al 2011].

3.1. Homocysteine and one-carbon metabolism

Elevated plasma homocysteine level has been proposed to be one of the risk factors for Alzheimer's disease [ZHUO et al 2011]. Homocysteine is a sulfur-containing non protein amino acid, produced in the methionine cycle, which is known as one-carbon metabolism. This biochemical pathway is regulated by folate, vitamin B_{12} and vitamin B_6, and leads to the production of S-adenosyl methionine (Illustration 5).

Being catalyzed by methionine synthase (MTR), which requires vitamin B_{12} as cofactor , 5-MTHF from dietary folate transfers a methyl group to homocysteine, forming methionine and tetrahydrofolate (THF). Methionine is then converted to S-adenosylmethionine (SAM), which serves as an universal methyl donor for various biological acceptors, such as DNA, RNA, proteins, neurotransmitters and phospholipids. After demethylation, SAM generates S-adenosylhomocysteine (SAH). The reversible hydrolysis of SAH leads to the formation of homocysteine.

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44 DNA methylation is a process of which S-adenosylmethionine (SAM) transfers a methyl group to the fifth carbon position of the cytosine pyrimidine ring base of a cytosine-guanine dinucliotide (CpG) and is catalyzed by DNA- methyltransferase (DNMTs).
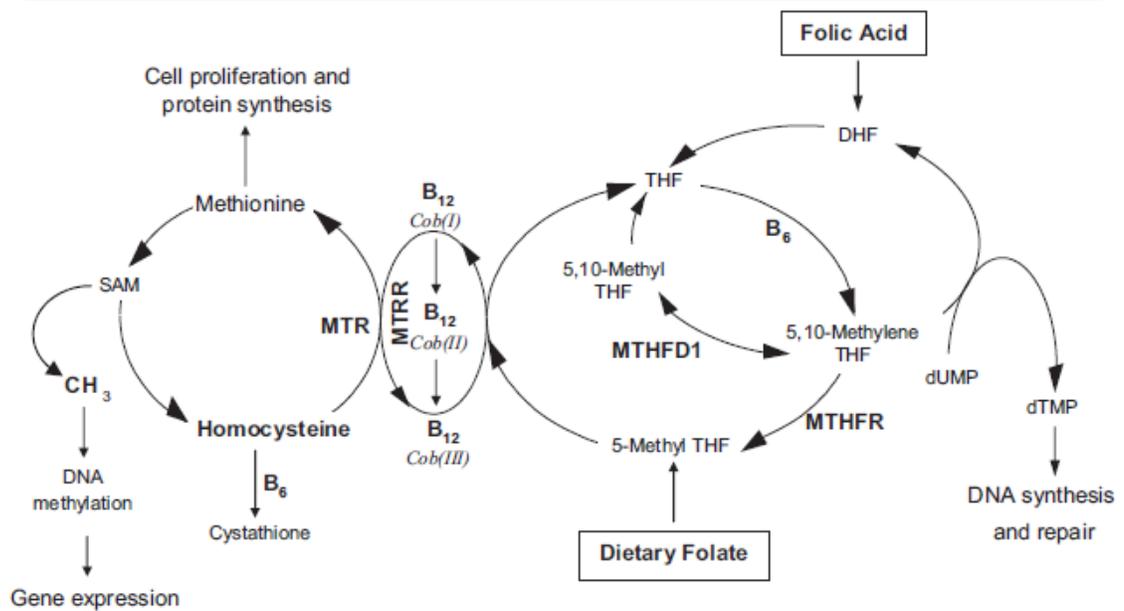
Illustration 5: One-carbon metabolism [FURNESS et al 2008]

DHFdihydrofolate ; THF tetrahydrofolate ; MTHFR methylenetetrahydrofolate reductase ; MTHFD1 methylenetetrahydrofolate dyhydrogenase ; MTR methionine synthase ; MTRR methionine synthase reductase ; SAM S-adenosylmethionine ;dUMP uracil ; dTMP thymine
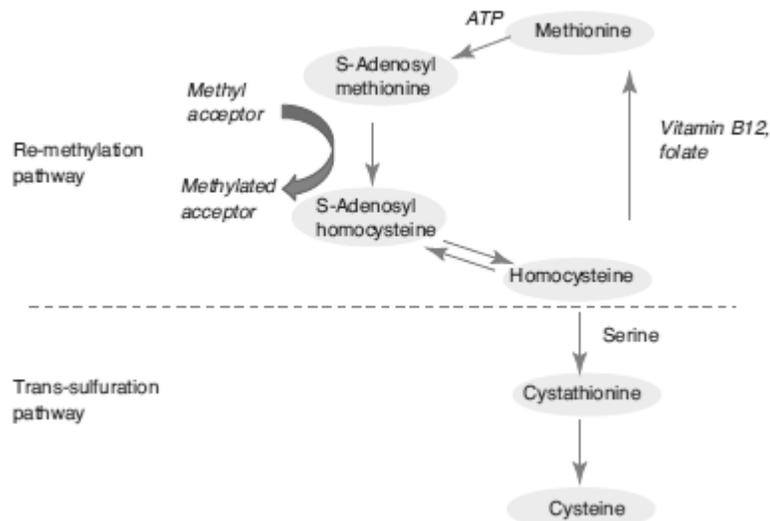
Illustration 6: 2 pathways of homocysteine conversion in one-carbon metabolism [ZHUO et al 2011]

Depends on methionine level, homocysteine is processed in two pathways; it is converted either to cysteine through trans-sulfuration pathway or remethylated to form methionine. When methionine levels are low, homocysteine is remethylated by the vitamin B_{12}-dependent enzyme methionine synthase (MS). When methionine levels are high, homocysteine is condensed with serine into cystathionine in a reaction catalyzed by the vitamin B_6-dependent enzyme, cystathionine beta synthase (CBS) [FUSO and SCARPA 2011]. Cystathionine then can be utilized to form glutathione (GSH)[45], which is an antioxidant peptide compound.

3.1.1. Methylation and chronic diseases

Methylation reactions is believed to have an important role in the pathology of many chronic diseases. In the brain, products of this methylation reactions are include neurotransmitters catecholamine, indoleamine, phospholipids and myelin, with SAM acts as an universal methyl donor.

Alternative methylation pathway in liver is betaine-dependent methyl transfer, which catalyzed by betaine-homocystein methyltransferase (BHMT). In this methyl transfer, dietary cholin is used as a substrate instead of folate [MEDINA et al 2001]. This pathway occurs mainly in liver and kidney, while the brain depends on folate-dependent methylation to eliminate homocysteine excess.

Disturbance in this biochemical pathways may lead to accumulation of homocysteine and SAH, decreasing SAM level and in turn reducing DNA methylation. This hypomethylation is believed to play a role in the

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45 Glutathione is an antioxidant compound, it consists of 3 peptides: cystein, glycin,glutamic acid.

neurodegenerative process [MEDINA et al 2001].

3.1.2. Hyperhomocysteinemia and neurons degeneration

The elevated plasma homocysteine is a risk factor for coronary artery diseases such as atherosclerosis and stroke. In the development of dementia and Alzheimer's disease, hyperhomocysteinemia is also a strong independent risk factor [SESHADRI et al 2002]. A systematic review showed, that when compared to healthy elderly, AD patients usually have high plasma homocysteine level in plasma and cerebrospinal fluid, but a decrease in folate and cobalamine plasma level [VAN DAM and VAN GOOL 2009] [CLARKE et al 1998].

Result from animal studies show the neurotoxic property of homocysteine, a direct injection into the rat's brain results in an increased beta amyloid level and tau phosphorylation, enhancing neuronal degeneration. In rat hippocampal neurons, homocysteine induces cell's apoptosis. The breaking of DNA strands, activation of poly-ADP-ribose polymerase and NAD depletion occurs rapidly after exposure to homocysteine, causing mitochondrial dysfunction, oxidative stress, and caspase[46] activation [KRUMAN et al 2000] .

Some authors suggested that the association of increased serum level of homocysteine and low folic acid with cognitive impairment in old age is likely to be a consequence of neurodegenerative disease and not a contributory cause [MOOIJAART et al 2005]. However, some studies propose several potential mechanisms, by which homocysteine may cause neurodegeneration in AD, such as oxidative stress, demethylation, cerebrovascular damage, endoplasmic reticulum stress, beta amyloid elevation and tau protein phosphorylation [ZHUO et

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46 The caspase is a cysteine-aspartic protease, an enzyme that play an essential roles in cell's apoptosis, necrosis and inflammation.

al 2011].

Moreover, homocysteine may promote oxidative stress by generating the formation of superoxide and hydrogen peroxide, or by reducing the antioxidant activity of glutathione (GSH), thus provoke the calcium influx and neurons apoptosis [HOGG 1999].

In the state of hyperhomocysteinemia, the production of S-adenosyl homocysteine (SAH) in the methylation reactions of one-carbon metabolism (Illustration 5) is elevated, increasing inhibition of DNA methyltransferase (DNMTs) [HULTBERG et al 2000]. Conversely, S-adenosylmethionine (SAM) level is depleted, thus resulting an overall decrease in cellular methylation [CAUDILL et al 2001]. Some authors argue, that the decreased SAM/SAH ratio[47] produce more critical damage than the increase of homocysteine concentration [ULREY et al 2005]. High SAH level and depleted SAM may demethylate the promoters of BACE-1 and presenilin 1, enhancing enzymatic activity of the secretases[48] and resulting in an increase in beta amyloid formation [SCARPA et al 2003]. Moreover, SAM activate the enzyme cysthathione beta synthase (CBS) and increase its activity about threefold. Low SAM concentration may lower CBS activity, thus directing homocysteine towards the transmethylation pathway and lesser glutathione production [SCARPA et al 2006]. Elevated homocysteine level may also support tau hyperphosphorylation. Demethylation of protein phosphatase-2A (PP2A)[49] cause a decrease in PP2A activity, resulting in tau hyperphosphorylation and neurofibrillatory tangles formation [SONTAG et al 2007][WANG et al 2007].

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47 SAM/SAH ratio is also known as methylation potential.
48 In the pathogenese of AD, ß-amyloid production from APP is regulated by the balance between secretases enzyme activities. APP is processed by γ- and α-secretases to non-amyloidogenic peptides, while γ- and β-secretases produce toxic aggregated amyloid beta fragments.
49 Phosphorylation of tau protein in the brain is regulated by a set of kinases and phosphatases.Several enzymes that regulate tau phosphorylation are glycogen synthase kinase 3ß (GSK3ß), phosphatidyl nositol 3-kinase (PI3K), mitogen-activated protein kinase (MAP).

Renal dysfunction, genetic polymorphisms[50] of the enzymes correlated with folate metabolism, and B vitamins deficiencies are some conditions that may lead to elevated homocysteine level [KASOHA 2010]. Lowering homocysteine level is believed to have beneficial effect for cognitive function, this may be achieved through B vitamins intake.

3.1.3. Role of nutrients in one-carbon metabolism

Nutrients can affect the progress of one-carbon metabolism through its function as the supply of metabolites (i.e. SAM, folic acid and B vitamins), also as elements to modify the DNA methyltransferase (DNMT) activity directly (selenium, cadmium and nickel) [SCARPA et al 2006].

Folate, cobalamine and vitamin B_6 have an important role as cofactor of enzymes in one-carbon metabolism. Since these vitamins are derived from dietary source, chronic deficiencies may cause disturbance of methylation process, and in turn induce neurodegeneration. Recent data shows that B vitamins deficiencies may lead to epigenetic modifications and subsequent deregulation of disease's related genes. In the culture medium of neuroblastoma cell, deprivation of cobalamine and folate increases beta amyloid production [FUSO et al 2005] and feeding mice with B-vitamin-deficient diet induces hyperhomocysteinemia and caused neurodegeneration [TROEN et al 2008].

50Polymorphisms in the genes coding for folate metabolism are investigated as AD risk factor. These genes are methylenetetrahydrofolate reductase (MTHFR), reduced folate carrier-1 (RFC1), methionine synthase (MTR), and cystathionine ß-synthase (CBS).

3.1.4. Homocysteine, folate, cobalamine plasma levels and cognitive functions

Indeed, plasma level of B vitamins from elderly subject with Alzheimer's Disease is often deficient. A systematic review from 22 studies concludes, that folate and cobalamine level of AD subjects is significantly lower than the control group. Although there is little data found for vitamin B_6, but 2 available studies recently conclude that there is no difference in vitamin B_6 plasma level of elderly with dementia compared to control healthy subjects [COPPEDÈ 2010] [LOVATI 2007].

Elevated homocysteine level is associated with poor performance of cognitive functions of nondemented elderly population in some case control studies [SOLFRIZZI et al 2006][RAVAGLIA et al 2003]. The result from the large prospective Framingham community study confirmed, that hyperhomocysteinemia may double the risk of developing dementia. Thus, some authors conclude that the increased level of homocysteine may precede the onset of dementia and it is a strong, independent risk factor for the development of dementia and AD [SESHADRI et al 2002].

Accordingly[51], plasma folate and cobalamin levels are associated with cognitive performance. High plasma folate is associated with better cognitive function and better performance on tests of psychomotor speed, although in some studies this relation is independent of homocysteine concentration [DE LAU et al 2007].

The results from National Health and Nutrition Examination Survey (NHANES) indicate the strong relationship between folate and vitamin B_{12} status. When cobalamin status is normal, a high serum folate is associated with the protection from cognitive deterioration. But the combination of low cobalamin status with high

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51 Plasma folate has an inverse correlation with plasma homocysteine level.

serum folate is related to anemia and cognitive impairment [SELHUB et al 2007]. Consistent with this finding, among the persons with low cobalamin status, high homocysteine levels are found at both very low and very high serum folate levels.

The reason why folate excess may interfere with cobalamin metabolism and cause hyperhomocysteinemia is still unclear. One theory postulates that folate may act as an oxidizing agent and accelerate the rate of oxidation of methionine synthase cob(I)alamin to methionine synthase cob(II)alamin or it may oxidize vitamin B_{12} to form a free radical thus inactivating methionine synthase [SELHUB et al 2007].

Aside from its function as coenzym in remethylation reaction of homocysteine to methionine, vitamin B_{12} also plays an key role in the isomerization of L-methylmalonyl-CoA to succinyl-CoA through the enzyme methylmalonyl-CoA mutase (MCM) in mitochondria. Cobalamin deficiency may cause the block in this isomerization reaction and result in methylmalonic acid (MMA) accumulation. Increased methylmalonic acid (MMA) concentrations often occurs in early stages of cobalamin deficiency before the decrease in plasma vitamin B_{12}, thus researches regard this to be early and specific indicators of functional vitamin B_{12} deficiency [KLEE 2000].

The decreased level of vitamin B status may not merely due to poor nutrient intake only, but also disturbance in B vitamins absorption and utilization[52] [FIORAVANTI et al 1997]. Atrophic gastritis limits the bioavailability of folate and cobalamine and cause a change in gastric emptying, lower secretion of intrinsic factor, impair the

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52 Other reasons for vitamin B12 deficiency are diseases such as pernicious anemia, colibacteria, tapeworm, or exocrine pancreas insufficiency, postgastrectomy states, hypochlorhydria, and altered peptic ability to impair cobalamin uptake. Moreover, resection of terminal ileum or infl ammatory bowel disease, sprue, coeliac disease or other abnormalities of the ileum may also result in B12 deficiency [WAHLIN et al 2001].

acid secretion in the stomach and resulted in impaired release of vitamin B_{12} from food proteins and peptides. Bacterial overgrowth in stomach may also increased pH level[53] and thus support malabsorption of these vitamins [SELHUB et al 2000].

3.1.5. Supplementation and dietary intervention to treat hyperhomocysteinemia and improve cognitive function

Epidemiology studies show that toxic effect of elevated plasma homocysteine occur over years, therefore the short duration of trials perhaps do not long enough to identify beneficial effect of homocysteine lowering therapy [BOTTIGLIERI 2005]. Cognitive impairment may indicate that the progression of neurons damage had occurred so severe that it is impossible to be cured by simple vitamin intake.

Nevertheless, considering the neurotoxicity of high plasma homocysteine level, intervention with high intake of homocysteine-lowering vitamins may reduce the risk or even prevent the onset of dementia, improve the cognitive function in elderly people and, at some point, may reverse the deleterious effect of hyperhomocysteinemia if initiated early in life. Reducing plasma homocysteine level may be achieved through supplementation and dietary intake of folate, cobalamine and vitamin B_6. SAM and betaine have also been proved to lower homocysteine.

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53 Folate is optimally absorbed at pH 6,3, atrophic gastritis normally increase intestinal pH.

3.1.6. Folic acid, cobalamine and vitamin B_6

Effectiveness of supplementation with a high dose of folic acid, vitamin B_6 and B_{12} to lower hyperhomocyssteinemia has been showed in some studies [SELHUB et al 2000]. Patients with elevated plasma homocysteine and mild-moderate dementia improved cognitive function with higher test scores after vitamin substitution, while demented patients with normal plasma homocysteine did not improve clinically in the test [NILSSON et al 2001]. Another randomized, double-blind controlled clinical trial on 409 individuals with mild to moderate AD showed that folic acid and B vitamins supplementation had no beneficial effect on the cognitive function, although they were effective in reducing the high homocysteine levels. The trial used 1000 µg of folate, 500 µg of vitamin B_{12}, and 10 mg of vitamin B_6 and was conducted for 2 years [MC MAHON et al 2006]. The short duration of the trial may limit the result to point out the effect of long term treatment [AISEN et al 2008].

As described above, folate supplementation should consider total homocysteine (tHcy) and methylmalonic acid (MMA) concentration in the plasma, since both tHcy and MMA are two functional indicators of vitamin B_{12} tissue status. Excessive folate intake through supplementation among the group of vitamin B_{12} deficient subjects may have adverse effect in lowering homocysteine.

Moreover, it seems that there is a threshold effect in the relationship between folic acid and plasma homocysteine concentration, above a certain dosage of supplementation, there is no additional effect on lowering homocysteine [DEL PARIGI 2006]. The minimum dosage of folate capable to reduce circulating homocysteine for about 25% is 0.8mg/day [WALD et al 2001] or 0.4mg/day [VAN OORT et al 2003].

3.1.7. Betaine supplementation

Betaine (trimethylglycine), like folate, serves as methyl donor and has plasma homocysteine lowering effect. The reaction converts homocysteine to methionine by the enzyme betaine-homocysteine methyltransferase (BHMT). Low plasma betaine level is associated with high fasting plasma homocysteine concentrations and vice versa [MELSE-BOONSTRA et al 2005].

Both remethylation pathways, namely folate-related and betaine-related methylation, may be interrelated, even though betaine methylation mainly occurs in kidney and liver. A choline deficient diet for 2 weeks decreases the hepatic folate concentration in rats, and a folate deficient diet result in depleted hepatic choline content. This suggests, that the limitation of one pathway may increase remethylation reaction via other pathway [MELSE-BOONSTRA et al 2005], thus making both pathways have significant role in controlling homocysteine level.

The betaine pathway may be more important in metabolizing homocysteine after a mealtime, due to its location in liver, while folate pathway may be crucial in maintaining fasting plasma homocysteine [CHIUVE 2007]. Supporting this theory is the evidence that betaine can lower homocysteine level after a methionine load, while folate substitution has no effect [STEENGE et al 2003]. On the other hand, fasting homocysteine level is decreased more by folate supplementation [VAN OORT et al 2003].

In the clinical setting, dose of >6g betaine per day is used to lower plasma homocysteine in patients with genetic defects in homocysteine metabolism. In healthy subject, the dose of 6g/d betaine decreases fasting plasma homocysteine by 10-15% and postmethionine loading plasma homocysteine by 40% [OLTHOF et al 2003]. Further, Olthof et al show that supplementation at the dose of 1,5g/d is

already effective to lower fasting plasma homocysteine.

In the body, betaine may be obtained from its precursor choline or from the diet. High dose supplementation of 2,6g/d choline in form of phosphatidylcholine in intervention trials, results in lower plasma homocysteine concentration in healthy subjects with mildly elevated plasma homocysteine [OLTHOF et al 2005]. Choline is then converted irreversibly into betain in liver and kidney by the enzyme choline oxidase.

According to Chiuve et al, who investigated 1477 women from NHS (Nurses' Health Study) , daily median intake of betaine and choline from dietary sources are 323 and 189 mg respectively, which may be too low to derive homocysteine lowering effect [CHIUVE et al 2007] .

3.1.8. S- adenosylmethionine supplementation

Evidence seem to support the protective effect of S-adenosyl methionine (SAM) against neurodegeneration. Decreased SAM level has been found in cerebrospinal fluid of Alzheimer's and depressed patients, also in post-mortem Alzheimers brain tissue [BOTTIGLIERI et al 1990].

The administration of SAM in human neuroblastoma cell line, results in downregulation of beta amyloid peptide production by inactivating the secretases through PSEN1 silencing [FUSO et al 2005].

Animal experiment using transgenic mice with genetically modified apoliprotein E (ApoE -/-) deficiency shows that supplementation of SAM results in a decrease of

oxidative damage by stimulating glutathione (GSH) system[54] [TCHANTCHOU et al 2005]. These transgenic mice undergo a more severe oxidative damage and cognitive impairment on low- folate diet than normal mice. They also display an elevated GSH level in brain tissue, possibly showing an impairment in the utilization of GSH [SHEA et al 2002]. Supplementation with SAM in ApoE -/- mice with folate deprived diet results in the restoration of glutathion S-transferase (GST) activity, reduced glutathione synthase (GS) transcription and reduced GSH levels to the level like those of normal mice feed with complete diet. This result prove, how diet may affect and support the remethylation reaction of critical gene expression, making genetic predisposition less harmful or delay [TCHANTCHOU et al 2005].

Interestingly, both control and ApoE -/- mice when fed with folate deficient diet, show a reduced SAM level in the brain, but yet normal mice do not show symptoms of neuropathology. Since ApoE -/- mice has a significant increase of S-adenosyl homocysteine (SAH), a decrease of the SAM/SAH ratio may inhibit GST activity in the brain, leading to more severe oxidative damage despite of excess antioxidant glutathione [TCHANTCHOU et al 2005].

Evidence from human trials is also promising. An epidemiological study shows, that test person's cognitive function is better in the group with higher SAM/SAH ratio [OBEID et al 2009]. Intervention study with small subject numbers (n=4) of Alzheimer's patients during 3-5 months trial with the dose of 400mg SAM 3 times daily, results in an increased plasma and CSF SAM concentrations and improved cognitive function, mood and speed of mental processing [BOTTGLIERI et al 1990]. On the other hand, another study shows no effect of 200mg-400mg/d intravenous SAM administration, although study duration of 2 weeks is considered too short to draw conclusion [COHEN et al 1988].

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54 SAM has a role in methylating substrates for GSH-dependent enzymes.

Recent small trial involving 7 AD subjects provide 1200mg oral SAM supplement daily for 12 weeks. Slight improvement of cognition tests is observed in all subjects, two improved moderately and none worsened in cognition nor behavior. moderate improvement of cognitive function after SAM intake [RUDOLPH et al 2011].

SAM is apparently well tolerated and has been used to treat depression and arthritis [MISCHOULON und FAVA 2002]. It holds a potential as therapeutic approach to prevent or delay progression of AD.

To date, there is still no data on humans that correlates either folate and homocysteine plasma status or brain SAM level, to the methylation profile of specific AD gene in the brain [COPPEDE 2010]. Research in this area is important, to clarify, whether or not epigenetic modifications are reversible and could be modulated through nutrients intake such as SAM and folate.

3.2. Thiamine

The connection between a chronic deficiency of thiamine and dementia symptoms can be seen in Wernicke- Korsakoff syndrome[55]. In the case of alcohol dementia, high dose administration of thiamine can reverse the neurological symptoms, thus understanding the mechanism of how thiamine induces neuronal damage may give a hope for the treatment of neurodegenerative diseases.

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55 Wernicke-Korsakoff syndrome is a dementia caused by chronic and excessive alcohol consumption. Plasma thiamine level is usually decreased in the group of alcohol dementia patients.

Alcohol and reduced intestinal resorption are risk factors for thiamine deficiency. Alcohol seems to reduce thiamine phosphorylation to thiaminepyrophosphat (TPP)[56] in brain. TPP is a cofactor for many enzymes, such as transketolase, pyruvate dehydrogenase complex (PDHC) and α-ketoglutarate dehydrogenase (αKGDH). These enzymes are involved in carbohydrates[57] and energy[58] metabolism, biosynthesis of neurotransmitters and also for the production of reducing equivalents used against free radicals [DROR et al 2010] [SINGLETON and MARTIN 2001].

There are indications, that the activity of these enzymes are reduced in thiamine deficiency and in neurodegenerative disorders, especially αKGDH [DROR et al 2010][BUBBER et al 2004]. In the brain of the thiamine deficient (TD) animal model, reductions of αKGDH are associated with a decreased aspartate, glutamate and γ-aminobutyric acid (GABA) but increased alanine level [BUTTERWORTH 1989]. Decreased activity of TPP-related enzymes may cause disturbance in brain glucose metabolism, energy shortage, mitochondrial dysfunctions and chronic oxidative stress [ZHANG et al 2011].

In relation with plaque formation, thiamine deficiency in wild type mice induces accumulation of cluster of dystrophic neurites, but without the morphology of amyloid plaque. Instead of amyloid plaques, the center of lesions are formed from necrotic debris [CALINGASAN et al 1995]. Moreover, accelerated beta amyloid production by promoting the activity of ß-secretase is observed in transgenic micel model [ZHANG et al 2011].

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56 As a coenzym in catabolic metabolism, thiamine exists in 3 forms in the body, free thiamine, thiaminetriphophat (TTP) , thiaminepyrophosphat (TPP) and thiaminemonophosphat (TMP).

57 In cytosol, the enzyme transketolase is involved in pentose phosphate pathway, generating the sugars deoxyribose and ribose.

58 PDH and αKGDH are mitochondrial enzymes, that involved in producing ATP , a major energy source for the cell.

Human trials result in concordance with animal experiment. A study of 38 elderly found that, the blood level of thiamine, TPP and TMP in AD patients are lower compared to the control group [GLASO et al 2004]. The TPP-dependent enzymes, αKGDH and transketolase, are found to have a decreased activity in the brain, while the levels of free thiamine and TMP are still normal, suggesting that TPP production may be impaired in the Alzheimer's brain rather than thiamine deficiency [MASTROGIACOMA et al 1996].

In animal models, administration of thiamine has successfully reverse TD-induced beta amyloid accumulation [ZHANG et al 2011], but the results of studies investigating the effect of thiamine supplementation on human AD patients are inconsistent. Mild beneficial effect was shown from one study with 3-8g thiamine per day [MEADOR et al 1993], while another study with 100 mg/d thiamine tetrahydrofurfuryl disulfide for 12 weeks found little effect [MIMORI et al 1996]. In contrast, a longer interventional study showed effect at all with 3g/d thiamine over 12 months [NOLAN et al 1991].

Considering the importance of thiamine in glucose and energy yielding metabolism, having sufficient thiamine status would be desirable, but the deficiency seems not only because of insufficient thiamine intake. Half of elderly is considered thiamine deficient, although consumed more than daily recommendation[59] [NICHOLS and BASU 1994]. Moreover, thiamine resorption decreases with age and single oral dose of thiamine higher than 2.5 to 5mg are largely unabsorbed [LU'O'NG and NGUYÊN 2011], suggesting that supplementation alone is ineffective to maintain sufficient thiamine status and activity of thiamine-dependent enzymes.

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59 In D-A-CH reference values , thiamin's recommended daily intake for elderly is 1mg/d.

Interestingly, dietary restriction[60] attenuates neurodegeneration in thiamine deficient (TD) mice [CALINGASAN and GIBSON 2000]. Oxidative stress seems to play the key role in the selective loss of neurons during TD and caloric restriction[61] protects neurons by inducing a low level stress, which then enhances free radical scavengers that protect neuron.

How far diet influences thiamine homeostasis in the case of neurodegenerative diseases will be an exciting area of research in the future.

3.3. Niacin

Dementia is one of the symptoms of pellagra[62], a disease caused by severe niacin deficiency, suggesting a possible correlation of dementia with this nutrient. Niacin[63] or vitamin B_3 is a collective term for nicotinic acid and nicotinamid. Nicotinic acid, nicotinamide and the newly identified nicotinamide ribose are salvageable[64] precursors of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which serve as coenzymes for many oxidation-reduction reactions [AMANULLAH and SEEBER 2010] and as substrate for NAD^+ consuming enzymes [BOGAN and BRENNER 2008]. In addition, amino acid

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60 In this study, diet is restricted gradually up to 60% of ad libitum intake.
61 More about the effect of caloric restriction on modulation of oxidative stress will be described in the antioxidant sub-chapter.
62 Symptoms of pellagra are dermatitis, diarrhea and dementia. Dementia usually presents in the last stage, in the form of confusion, hallucinations, psychosis, memory loss, apathy and depression. Untreated, pellagra may lead to death.
63 Niacin is an abbreviation of nicotinic acid vitamin, this term is made to differentiate nicotinic acid with nicotine in tobacco.
64 Salvage pathway is the opposite of de novo synthesis, where complex molecules are synthetized from simple ones. Salvageable molecules undergo a recycling reaction, in which degraded substances are used to form or recover the starting material, e.g. in nucleotide metabolisms.

tryptophan[65] may also be converted to NAD through de novo pathway, which requires vitamin B_2 and B_6[66] as coenzymes.

Conversions of tryptophan, nicotinic acid, nicotinamide or nicotinamide ribose to NAD involve different biosynthetic pathways, which explain why each of them has different physiological and effects. Nicotinamide for example, does not reduce cholesterol nor cause skin flushing if consumed in high doses, where nicotinic acid does.

Nicotinic acid

Nicotinic acid in pharmacological dose[67] of 1,5g/d to 6g/d has been used to lower total cholesterol level, LDL, TG and increase HDL levels, thus lower the risk of atherosclerosis. Since increased cholesterol level is one of the risk factor of developing Alzheimer's, nicotinic acid may prevent cognitive deterioration through its function as cholesterol-lowering agent thus improving cardiovascular risk factor.

As the reason why nicotinic acid improves cholesterol level may be because the requirement for elevated NAD^+ biosynthesis depends on sirtuin[68], whose function is inhibited by nicotinamide [BOGAN and BRENNER 2008].

Nicotinamide

At the cellular level, nicotinamide functions include enhancing energy metabolism, activating protein kinase B and inhibit poly(ADP-ribose)polymerases (PARPs) and

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65 60 mg tryptophan is equal to 1mg niacin equivalent.

66 Increased demand of vitamin B6, e.g. from anti-tubercolosis medications such as isozianid andpyrazinamide, inhibit the conversion of tryptohan to niacin thus may lead to deficiency.

67 High dose of niacin has been reported to cause reddening of the skin, known as flushing, as well as dry skin and skin rashes.

68 Sirtuins are protein, which functions as enzymes for histone acetylation and ADP ribosylation reaction.

sirtuins [YING 2007].

In mice model of Alzheimer's disease, Green et al observes, that nicotinamide does not affect beta amyloid pathology, but inhibits brain sirtuin (SirT2) deacetylation and therefore increase acetylated α-tubulin level in the brain. A high acetylated α-tubulin concentration is associated with increased microtubule stability [GREEN et al 2008]. Furthermore, nicotinamide significantly reduce Thr231-phosphotau[69] level. Phosphorylation of tau at Thr231 marks the tau protein for degradation, preventing its aggregation and accumulation.

In cognitive tests, nicotinamide-treated mice are observed to have improved spatial learning skills and restore short and long term memory. But molecular and cognitive effect of nicotinamide only occurs to mice with mild to moderate pathology. In the late stage, where aggregation and accumulation of tau has occured, nicotinamide has no effect in removing Thr231-phosphotau [GREEN et al 2008]. Moreover, nicotinamide regulates the activity of NAD^+ consuming enzymes, by its role as NAD^+ precursor and by direct enzyme inhibition [BOGAN and BRENNER 2008].

Beneficial effects of niacin derivates are postulated to be related to NAD^+ biosynthesis, since it has essential roles as hydride donor and acceptor in many redox[70] reactions of biological processes, such as energy production, synthesis of fatty acids, cholesterol and steroids. And recently, enzyme mediated and non-redox functions of NAD^+ have been discovered. Mitochondrial functions, calcium homeostasis, gene expression, DNA repairment, apoptosis, antioxidative reactions and neurotransmission are influenced by the activity of NAD^+ (Illustration 7).

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69 Thr-231 phosphotau affects microtubule polymeration and its concentration in CSF is used as biomarker for AD [CHO and JOHNSON 2004].
70 Oxidation reduction.
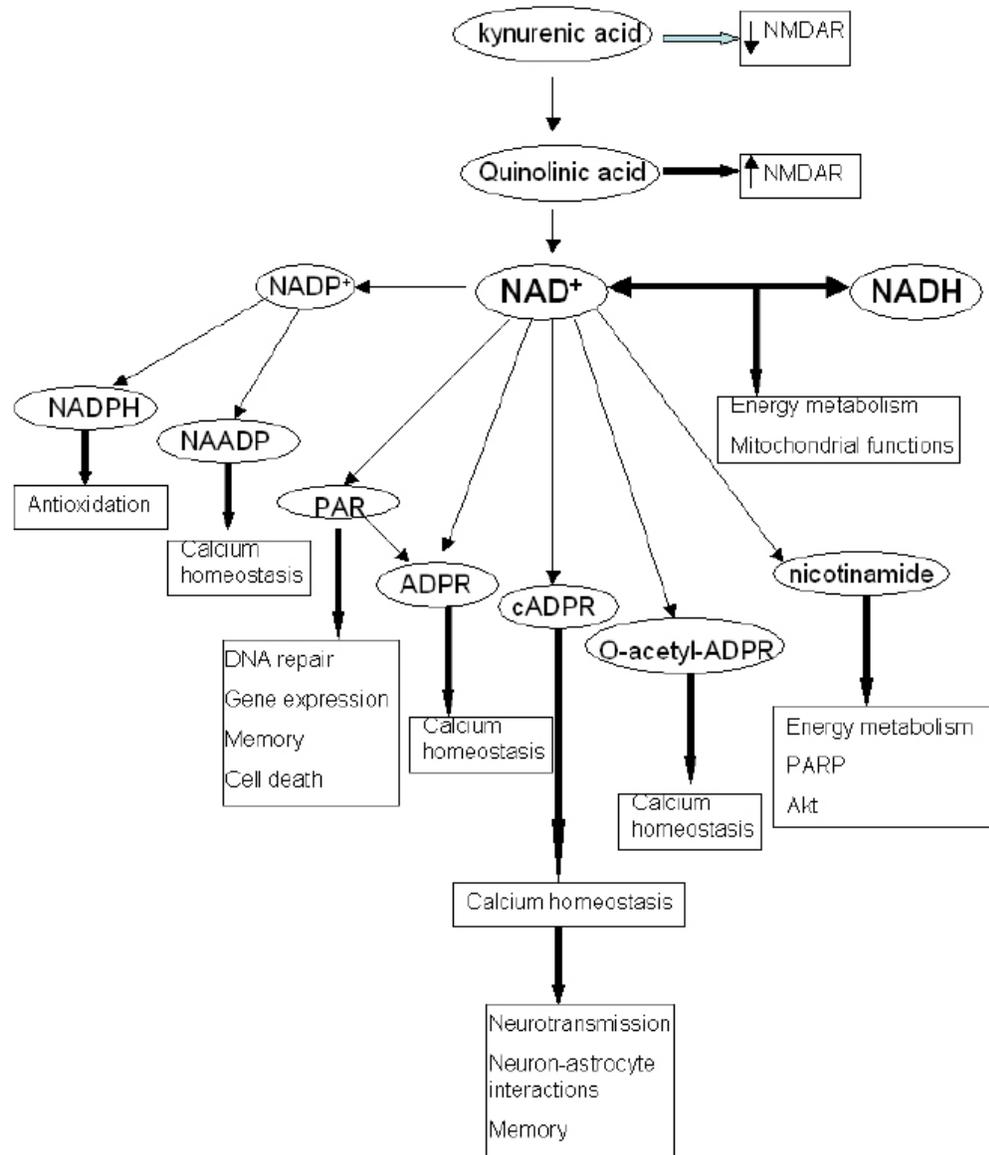
Illustration 7: Biological process and pathways mediated by nicotinamide adenine dinucleotide [YING 2007].

NAD^+ is utilized by the enzyme sirtuins, particularly SIRT1[71], as a substrate to catalyze deacetylation of histone[72]. This reaction releases nicotinamide and forms a metabolite 2'-O-acetyl-(ADP) ribose as well as a deacetylated lysine product. Overexpression of sirtuin genes (silent information regulator two protein) is also postulated to be responsible for lifespan extension in caloric restricted diet [GUARENTE and PICARD 2005].

Human studies also support the findings from animal studies about the protective effect of niacin on development of AD and cognitive decline. A prospective study from Morris et al of 3718 elderly, showed that the consumption of niacin may decrease the risk of Alzheimer's disease. Niacin intake from food and supplements, niacin intake from foods only and tryptophan intake are inversely associated with incident of AD. Moreover, higher intake of niacin from foods is associated with slower annual rate of cognitive decline [MORRIS et al 2004].

Another randomized controlled trial with 26 AD subjects investigated the supplementation of 10mg stabilized oral NADH per day during 6 months period. The result showed a significantly higher scores on cognitive test in the intervention group, and better performance on verbal fluency, visual constructional ability and abstract verbal reasoning when compared to placebo. But there is no differences in measures of attention, memory and in clinical dementia rating [DEMARIN et al 2004].

Considering its important role in various biological metabolisms, niacin may present another possible approach of epigenetic modification to prevent neurodegeneration.

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71 There are 7 family members of sirtuins identified in human;SIRT1 to SIRT7.

72 Histone acetylation and histone deacetylation reaction, which removes acetyl group from lysine residues within protein, regulates chromatin condensation and gene transcription involving the histone acetyltransferases (HATs) and histone deacetylases (HDACs) as key enzymes. One of HDACs class, namely silent information regulator two (Sir2) is NAD+ dependent.

3.4. Lipids: Cholesterol, ω-3 fatty acids and phospholipid

3.4.1. Cholesterol

Brain is an organ with the highest cholesterol content in the body. Almost 25% of the unesterified cholesterol present in the plasma membranes of glial cells, neurons, and in the specialized membranes of myelin [DIETSCHY and TURLEY 2001]. In CNS, cholesterol is required for the synthesis of neuron synapses and myelin sheath, regulation of neuronal membrane plasticity and also the regulation of the membrane bound enzymes, receptors and ion channels [MATHEW et al 2011].

The first link between cholesterol and AD come from the observation, that allele ε4 of the Apolipoprotein E (ApoE) is a risk factor for the disease. ApoE is the main cholesterol transport protein in the brain, that coordinate the mobilization and redistribution of cholesterol and phospholipids in central nervous system. Although the exact mechanism of how cholesterol may influence the development of neurodegenerative diseases is still inconclusive, recent researches conclude that there may be a disturbance in the cholesterol homeostasis, which is maintained by the balance between cholesterol transport (by ApoE/ApoE receptor pathway), cholesterol synthesis (by HMGR[73] pathway) and cholesterol elimination from the brain.

Altered cholesterol homeostasis can modulate beta amyloid production and accumulation [PATEL and FORMAN 2004]. High brain cholesterol level is showed to increase the amount of beta amyloid generation in vitro [EHEHALT et al 2003]. But other study found that moderate cholesterol reduction in hippocampal neurons results in the enhancement of APP-ß-cleavage and beta amyloid production

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73   HMGR is 3-hydroxy-3-methylglutaryl coenzym A reductase

[ABAD-RODRIGUEZ et al 2004]. Apparently, the distribution of cholesterol in plasma membrane is more important than total cholesterol level [BURNS et al 2006].

The reason why Aβ production is sensitive to cholesterol levels is, because the activity of β- and γ-secretase complexes are very dependent on cholesterol metabolism [WOLOZIN 2004]. Cholesterol binds to APP at the alpha secretase cleavage site, thus favoring ß-secretase activity and leading to increased production of beta amyloid [YAO and PAPADOPOULOS 2002]. Thus inhibiting cholesterol synthesis through cholesterol-lowering medications is thought to reduce Aß production.

Indeed, epidemiological data showed that there was up to a 70% lower prevalence and incidence of AD in subjects taking statins, a cholesterol-lowering drug [JICK et al 2000]. This result lead to the assumption , that high plasma cholesterol level predisposes for AD, and therefore lowering circulating cholesterol level may lead to a reduced risk of AD.

But the mechanism of how high plasma cholesterol may influence cellular cholesterol level and affect the development of neurodegenerative diseases, is still unknown. Experiment in rabbits showed that brain cholesterol level is not affected by increased dietary cholesterol [GHRIBI et al 2006]. This may be due to incapability of plasma cholesterol to cross blood brain barrier [PFIEGER et al 2003]. Brain cholesterol is synthesized in situ from glial cells, and thus independent from variations that occur in plasma level [LEDESMA and DOTTI 2006].

If cholesterol level in brain does not affected by blood plasma cholesterol, then how hypercholesterolemia become a risk factor for AD? Ledesma and Dotti

assume, that high cholesterol plasma level may lead to AD through a secondary event, such as poor oxygenation of the brain due to cholesterol-clogged blood vessels. Subsequently, statins would reduce pathology of AD not because of the inhibition of cholesterol brain synthesis nor the reduction of the amount of periphreral blood cholesterol reaching the brain, but because of the overall improvement of peripheral and cerebral circulation and its anti-inflammatory property [LEDESMA and DOTTI 2006].

3.4.2. Fat intake – the role of dietary fats in AD

In animal experiments, high cholesterol diet is associated with higher amyloid disposition [MATHEW et al 2011] [SHIE et al 2002], intraneuronal accumulation of hyperphosphorylated tau [RAHMAN et al 2005] and decreased relative cerebral blood volume[74] (rCBV) [HOOIJMANS et al 2009], suggesting a connection of dietary fats with the neurodegeneration in AD. Although the exact mechanisms are still uncertain, at least dietary fats intake has an influence on plasma cholesterol level, since diets with a high ratio of saturated fat to polyunsaturated or monounsaturated fats have been proved to lead to a poor plasma cholesterol profile [MORRIS 2009].

Three prospective studies in Chicago, New York and Rotterdam reported a connection between fats intake and the incident of Alzheimer's disease. In the Chicago Health and Aging Project (CHAP), Morris and colleagues conclude that intakes of saturated fat and trans-unsaturated fat were positively associated with the risk of Alzheimer's disease, while intakes of ω-6 polyunsaturated fatty acid and monounsaturated fatty acid were inversely associated . Further, according to this study, total fat, animal fat and dietary cholesterol were not correlated with the

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74 Relative cerebral blood volume

development of Alzheimer's disease [MORRIS et al 2003].

The New York study by Luchsinger et al found evidence of a greater risk of AD in subjects with higher intakes of total fat and saturated fat and either homozygous or heterozygous for the ApoE ε4 allele, but no evidence found of an association with the intake of polyunsaturated fat [LUCHSINGER et al 2002].

In the Rotterdam Study, the risk of AD increased with higher intake of total fat, saturated fat and cholesterol after 2 years of follow-up [KALMIJN et al 1997], but after 6years of follow-up, none of dietary fats was associated with AD [ENGELHART et al 2002]. Results from Italian Longitudinal Study on Aging reported the potential of monounsaturated and polyunsaturated fatty acids to prevent cognitive decline [SOLFRIZZI et al 2006].

Although data from human studies are unclear , whether or which dietary fats affect cognitive function in older age, studies from animal experiments and cell culture seem to support the role of lipids in pathology of neurodegenerative diseases.

3.4.3. Polyunsaturated fatty acids (PUFAs)

Neuron membranes are rich in polyunsaturated fatty acids (PUFAs), including the ω-3 fatty acid docosahexaenoic acid (DHA) and ω-6 fatty acid arachidonic acid (AA). In the central nervous system, PUFAs play an important role in the structural and functional maintenance of neuronal membranes, neurotransmission and eucosanoid biosynthesis, as well as the maintenance of membrane fluidity, modulation of ion channels, receptors and ATPases. The composition of these fatty acids in brain's membrane seems to reflect that of the dietary source

[HOOIJMANS and KILIAAN 2008] [YOUDIM et al 2000].

Arachidonic acid (AA)

Arachidonic acid (AA) belongs to the group of ω-6 fatty acids. Through its metabolites prostaglandins, thromboxanes and leukotriene, AA is a mediator of inflammatory pathways. Results from cell culture and animal experiment suggested , that AA and its metabolites are involved in the production of beta amyloid, thus affect the pathogenesis of AD. Mice supplemented with 2% AA showed higher levels of amyloid plaques in the brain [AMTUL et al 2011].

Docosahexaenoic acid (DHA)

In vitro and in animal models, DHA has been shown to exert neuroprotective, antioxidant, antiinflammatory and beta-amyloid-reducing activities [COLE and FRAUTSCHY 2010].

But in human studies the link between dietary intake of fish or DHA and the risk of dementia including AD is less consistent. A systematic review from 12 studies conclude that the results varied greatly, therefore no definitive link could be drawn between low DHA intake and loss of cognitive function during aging [PLOURDE et al 2007][Maclean et al 2005]. On the other hand, the protective role of fish intake against the risk of AD is confirmed in some large prospective studies such as CHAP [MORRIS et al 2003], Rotterdam study [KALMIJN et al 1997] and Three City study [BARBERGER-GATEAU et al 2007]. Statistically, fish intake has stronger association with risk of dementia and AD than DHA intake [CUNNANE et al 2011].

Since lower fish consumption is associated with the risk of AD, one would presume that AD patients have a lower blood concentration of DHA, but the data on blood parameter of DHA are also inconsistent. Heude et al reported lower plasma DHA in AD patients [HEUDE et al 2003] while other studies mean plasma DHA is not different from control subjects [CUNNANE et al 2011]. In the Framingham study, high plasma phosphatidylcholine (PC) DHA correlated with 47% risk reduction of AD [SCHAEFER et al 2006], and in other study erythrocyte phosphatidylcholine DHA is 400% lower in AD patients [SELLEY et al 2007] , leading to an assumption that PC DHA may be a stronger predictor of risk reduction as total DHA level [COLE and FRAUTSCHY 2010]. Data on brain DHA level in AD patients vary considerably, three studies indicate that DHA may be markedly lower in hippocampus in AD [CUNNANE et al 2011].

A randomized clinical trial investigated the protective effect of fish consumption for primary prevention of AD. A group of 302 healthy elderly received DHA and EPA supplement either 1800mg/d or 400mg/d or placebo for 26 weeks. There is no difference in any cognitive domain among 3 groups, only ApoE ε4 carrier improved with fish oil consumption in cognitive domain of attention [VAN DE REST et al 2008]. While one smaller study of 49 healthy elderly women supplemented with either DHA, with or without lutein, and placebo, resulted in improved verbal fluency in DHA group [JOHNSON et al 2008].

A systematic review of 11 observational studies and 4 clinical trials on AD patients concludes that ω-3 fatty acids may be effective in slowing cognitive decline for elderly without dementia, but is not recommended for those who already developed dementia [FOTUHI et al 2009]. In patients with very mild AD, supplementation of DHA may have positive effects on cognition [FREUND-LEVI et al 2006]. On the other hand, Kotani et al found no benefit of DHA supplementation on cognitive function [KOTANI et al 2006].

Study	Design	Inclusion criteria	ω-3 intake and measurement	Outcome measures	Results
Etude du Viellissement Arteriel (France)	4-year prospective cohort study; n=246; mean age 68	Normal volunteers	Measurement of erythrocyte membrane fatty acid content (total ω-3 PUFA, ω-3:ω-6 ratio, DHA:AA ratio)	Cognitive decline measured with MMSE score	High proportion of plasma ω-3 fatty acids level were associated with 41% less cognitive decline; results were statistically significant for DHA level and DHA:AA ratio, but not EPA levels
Chicago Health and Aging Project (USA)	6-year prospective cohort study; n= 3718 ; mean age 73	Normal cognition	Fish meals per week (zero, one or two)	Change in rate of global cognitive decline estimated from mixed models	Rate of cognitive decline per year decreased by 10-13% among subjects who consumed one or more fish meals per week. But the benefits of eating fish meals could not be accounted for by the amount of dietary DHA or EPA
Zutphen Elderly Study (The Netherlands)	5-year prospective cohort study ; n=210 ; mean age 75	Men with no dementia	Fish consumption based on FFQ; levels of DHA and EPA from both fish and other sources	Cognitive decline measured by MMSE	A linear trend was seen between high intake of EPA plus DHA and reduced 5-year cognitive decline. 400mg of DHA plus EPA per day was associated with a 1,1-point reduction in cognitive decline over 5 years

Table 8: Observational studies of the connection between fish consumption or n-3 fatty acids and cognitive functions in normal person [FOTUHI et al 2009]

Abbreviations: FFQ = Food Frequency Questionnaire

Study	Design	Inclusion criteria	ω-3 intake and measurement	Outcome measures	Results
Terano et al 1999	12-month RCT: n=20	Elderly individuals with mild-to-moderate vascular dementia (MMSE score 15-22) living in a home for the elderly	Placebo: no supplementation; treatment : 12 months of 4,32g DHA/d	Cognitive decline measured by MMSE and HDS-R	DHA supplementation significantly reduced the rate of cognitive decline over 3 months and 6 months of follow-up, but not over 12 months
Kotani et al 2006	90-day RCT; n=39	Subjects with amnesia owing to mild cognitive impairment, AD or organic brain lesions	Placebo: 90 days of 240mg per day olive oil; treatment: 240mg DHA and AA per day and 6,4mg asthaxanthine per day	Cognitive dysfunction measured by repeatable battery for the assessment of neuro-psychological status	No significant benefit for patients with AD; patients with organic brain lesions showed improvement in both immediate and delayed memory. Patients with MCI assigned to treatment improved their attention and immediate memory, but no change was noted in their delayed memory
Freund-Levi et al 2006 (OmegAD study)	12-month RCT; n=174	AD according to DSM-IV; MMSE score 15-30; living in own home	Placebo: 6 months of placebo followed by 6 months of DHA and EPA; Treatment : 12 months of DHA and EPA	Cognitive decline measured by MMSE and cognitive subscale of the AD assessment scale	No statistically significant difference in MMSE score between two groups at 6-month and 12-month time points. Statistically significant benefit in subgroup of patients with very mild AD; that is MMSE score >27
Van de Rest et al 2008 (MEMO study)	26-week RCT; n=302	>65 years old with MMSE score >21; not on dementia or depression medications	DHA-EPA 400mg or DHA-EPA 180mg versus placebo (oil capsule); serum DHA and EPA measurement	Cognitive function and mental well-being assessed by word learning test, forward and backward test of the Wechsler digit span,	No statistically significant change was noted in any of the cognitive domains for either low-dose or high-dose fish oil supplementation compared with placebo

				trail making test versions A and B, Stroop color-word test and verbal fluency test	

Table 9: Clinical trials of the effects of ω-3 fatty acids and either onset of dementia or AD or changes in cognitive performance [FOTUHI et al 2009].

These contradicting results may be caused by biological issues. Fish as the source of ω-3 PUFAs may be contaminated with heavy metals such as mercury, that may be involved in the pathological mechanism of neurodegeneration. [MONET-TSCHUDI et al 2006]. Moreover, fish contains not only ω-3 fatty acids, other nutrients such as fish protein, selenium and vitamin B_{12} may also provide protective effect against AD, through antioxidative and homocysteine-lowering properties [CUNNANE et al 2011].

Methodological issues such as the differences in the subtypes, dosage and duration in consumption of ω-3 fatty acids or fish, the genetic and environmental heterogeneity of subject persons, as well as different measurement and diagnostic tools used in the trial may affect the outcome [CUNNANE et al 2011].

Future research may also consider intake of another fatty acids in addition to DHA , especially ω-6 fatty acids, since their status and functions are strongly correlated[75]. Perhaps is the association of AD with low DHA intake is rather a question of too much ω-6 fatty acids consumption [CUNNANE et al 2011]. Lowering ω-6 fatty acids intake may modulate the ratio of membranes ω-6:ω-3 fatty acids, and this ratio is important to maintain normal brain function [HAAG 2003].

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75 ω-3 fatty acids DHA and EPA compete with ω-6 fatty acids ARA for the sn-2 position on the membrane phospholipids.

3.4.4. DHA and brain glucose metabolism

In recent studies, DHA has been shown to have an important role in brain glucose utilization. In DHA deficient mice, endothelial and astrocyte GLUT1[76] at the blood brain barrier is decreased, suggesting that glucose transport into the brain is disturbed. Evidence from literature pointed that global cerebral metabolic rate for glucose (CMRg) is ~20-25% lower in AD, with a more marked difference in some cortical regions [CUNNANE et al 2011].

Dietary supplementation with DHA increases GLUT 1 expression in rats brain, indicating the positive correlation between DHA level and glucose transporter expression in the brain [PIFFERI et al 2007]. Since glucose is the main fuel for neurons, perturbed glucose transport system may lead to cell's energy deficiency. Hypothesis emerges that glucose deficient neurons are forced to use ketone bodies as fuel. However, ketogenic response appears to be less efficient in the case of glucose intolerance, such as in type 2 diabetes and insulin resistance, both predispose to AD [PASQUIER et al 2004]. According to this hypothesis, cell's catabolic pathway of gluconeogenesis is the last effort of neurons to obtain fuel. If this is true, then increasing brain fuel availability through ketone supplements or ketogenic diet, may diminish the risk of further cognitive decline, if implemented before symptoms develop [CUNNANE et al 2011].

3.4.5. Ketogenic diet

Ketogenic diet consists of high-fat (up to 80-90% of total energy intake), low-carbohydrate and adequate protein meals. Low glucose intake forces the liver to

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76 Glucose transporters GLUT1 and GLUT3 are responsible for glucose uptake from blood vessel through blood-brain barrier into the brain's neurons.

utilize fats and produce ketone bodies such as ß-hydroxybutyrate, acetoacetate and acetone, and use them as main energy source. The diet is usually used for treating epileptic children, and in most cases this diet is effective to reduce seizures [GASIOR et al 2006].

The precise mechanism is still unclear, neuroprotective effect may be the result from enhance energy reserves of neurons to withstand metabolic stress. In the cellular level, a larger mitochondrial load and a more efficient energy fuel are observed in mice brain cell treated with ketogenic diet. Anti-inflammatory and antioxidative mechanisms are also postulated as one of the benefits of ketone bodies [GASIOR et al 2006].

In transgenic mice, ketogenic diet high in saturated fat (79%) and very low carbohydrate (0,76%) significantly reduce total brain beta amyloid levels by 25% [VAN DER AUWERA et al 2005]. The decreased beta amyloid is accompanied by weight loss and ketone bodies production. The author conclude, perhaps it was not fats in the diet that increases Aß level, but levels of total calories, carbohydrate restriction or the metabolic state of the animal.

In a study by Reger and colleagues, improvement of memory performance in AD patients during acute administration of medium-chain triglycerides was positively correlated with plasma levels of ß-hydroxybutyrate. Increased plasma ß-hydroxybutyrate is also observed in ketogenic diet, thus it is expected that ketogenic diet would also have beneficial disease-modifying activity in AD [REGER et al 2004].

At present, evidences are insufficient to conclude that ketogenic diet may be beneficial in the case of AD. Further researches and clinical trials are required to understand the mechanisms and optimal implementation of the diet that minimize

side effect[77].

3.4.6. Trans fatty acid (TFA)

High intake of dietary trans fatty acid increases TFA concentration in the brain and modify the brain fatty acid profile. Brain DHA concentration is decreased in mice fed with 43% TFA of total fatty acids intake, suggesting that TFA may not directly involved in pathology of AD [PHIVILAY et al 2009]. In a epidemiological study, TFA is positively associated with the risk of AD; individuals consuming ~4,8g TFA/day had a fivefold higher relative risk of developing AD than those who ate ~1,8g/day of TFA [MORRIS et al 2003]. But in transgenic mice model of AD, TFA does not seem to affect the level of beta amyloid , tau protein and synaptic markers [PHIVILAY et al 2009]

In conclusion, available data suggests that fats composition in the diet may have an important role to maintain proper brain function and prevent the pathogenesis of Alzheimer's disease. Since fats are consumed in combination with other nutrients in the diet, interaction of fats with other fatty acids and other nutrients such as antioxidants may be more effective than the intake of one fatty acid alone. Whether dietary fats benefit AD patients in early stages and could be implemented as part of therapy or not, is still inconclusive. Further research may consider macronutrient profile[78] on the diet, when examining the effect of dietary fat on biological processes [VAN DER AUWERA et al 2005].

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77 Due to its high content of fats, ketogenic diet is difficult to maintain, and is associated with adverse effects on bone health and liver [FREEMAN et al 2006].
78 Ratio of fat , protein and carbohydrate in the total energy intake.

3.5. Antioxidants in prevention and treatment of Alzheimer's Disease

Evidences indicate that oxidative stress excessively occur in the brain of AD. Intake of antioxidants from diet is thought to decrease the deleterious consequences of reactive oxygen species (ROS) and has been proposed to prevent cognitive decline, also as treatment for MCI and AD [BEHL and MOOSMANN 2002] [MECOCCI and POLIDORI 2011].

Antioxidants can be subdivided in enzymatic[79] and non-enzymatic forms, direct and indirect[80] , also endogenous and exogenous antioxidants. Non-enzymatic antioxidants, which are known as free radicals scavengers, such as vitamin C, vitamin E, polyphenols, carotenoids, flavonoids have been tested in clinical trials to investigate their efficacy for prevention or treatment of AD.

Compounds such as flavonoids in tea (epigallocatechin gallate EGCG), polyphenol compounds in wine (resveratrol), curcumin in turmeric, ginkgo extract and other phenolic compounds with antioxidative and anti-inflammatory effects, may have potential as therapeutics to attenuate or to prevent neurodegeneration.

3.5.1. Antioxidant vitamins

Vitamin E refers to eight different isoforms, which consist of saturated tocopherols (α, β, γ, δ) and unsaturated tocotrienols (α, β, γ, δ). To date, only α-tocopherol has been extensively investigated in randomized clinical trial, although each form

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79 Enzymatic antioxidants are enzymes , such as superoxide dismutase (SOD), catalase and glutathione peroxidase, which scavenge and break down free radicals.
80 Chelating agents, which bind metals ion and prevent formation of ROS, are considered indirect antioxidants.

has unique biological functions, e.g. antioxidative and anti-inflammatory activity, also modulating different signalling pathways [REITER et al 2007]. Compared to α-tocopherol , γ-tocopherol is more effective in scavenging reactive nitrogen species and tocotrienols are more efficient in neutralizing free radicals [SEN et al 2007]. Moreover, α-tocotrienol seems to attenuate the arachidonic acid cascade leading to oxidative brain injury and inhibit the glutamate-induced neurotoxicity by modulating phospholipase A2 activity [MANGIALASCHE et al 2011] [KHANNA et al 2010]. The neuroprotective effect of vitamin E seems to be related to the combination of different forms of tocopherols and tocotrienols.

High plasma levels of vitamin E is associated with a reduced risk of AD in advanced age. Levels of all forms of vitamin E are lower in the plasma of AD and MCI patients when compared with the healthy elderly [MANGIALASCHE et al 2011] [MORRIS et al 2005], indicating the connection of these vitamins' status with pathology of neurodegeneration.

Vitamin E crosses the blood brain barrier and accumulate at therapeutical levels in the central nervous system. At the molecular level, vitamin E is postulated to reduce lipid peroxidation and beta amyloid deposition [MECCOCI and POLIDORI 2011] [SUNG et al 2004].

However, the results from observational studies investigating vitamin intake and the risk of AD were inconclusive. The Cache County Study [ZANDI et al 2004], the Washington-Heights-Inwood Columbia Aging study [LUCHSINGER et al 2003] and Women's Health Study showed no benefit nor significant reduction in AD risk. On the other hand, the Honolulu-Asia Aging study [MASAKI et al 2000], the Chicago Health and Aging Project [MORRIS et al 2002], the Nurses' Health Study [GRODSTEIN et al 2003] and the Rotterdam Study [ENGELHART et al 2002] indicating positive correlation between vitamin intake and risk of developing AD.

Data about the implementation of vitamins in the treatment of AD is also unclear. One randomized double-blind and placebo controlled study from Sano et al, 341 AD patients were given 2000IU vitamin E in the form of α-tocopherol each day for two years. Result showed a delayed AD progression and delayed admission to nursing home for vitamin E group, but no effect on MMSE-score [SANO et al 1997]. In another trial with 769 MCI subjects, Peterson et al indicated that vitamin E has neither cognitive effect nor benefit in patients with MCI [PETERSEN et al 2005].

Brewer interprets these studies results as unreliable, due to inappropriate dose, timing and monotherapy [BREWER 2010]. High dose of antioxidants may have adverse effect, according to Miller and colleagues, long-term use of vitamin E supplement above 400IU may increase mortality [MILLER et al 2005]. Moreover, starting antioxidants therapy in patients with AD may be too late, since neurons is already degenerated [BREWER 2010]. The use of monotherapy may be insufficient, since α-tocopherol used in many clinical studies only present modest protective effect.

The neuroprotective effect of vitamin E seems to be related to the combination of different forms of tocopherols and tocotrienols [MANGIALASCHE et al 2011]. Another argument against monotherapy of vitamin is, that vitamin E needs vitamin C for antioxidant regeneration.

A case control study assessed vitamin C intake and compared its plasma level among 4 groups of AD patients; namely severe and moderate AD patients within community setting, AD patients in hospital and control subjects. Decreased plasma vitamin C was found in all AD subjects compared to control, and its reduction was in proportion to the degree of cognitive impairment. Interestingly, all the subject

persons in this trial took the same quantity of vitamin C, thus the reduction in plasma level could not be caused by lower intake [RIVIÈRE et al 1998].

Considering the synergic effect of both vitamins, some studies investigate the supplementation of vitamin E and C in connection with dementia prevalence. Zandi et al found that the combination of vitamin C and E supplements was associated with a lower prevalence of dementia [ZANDI et al 2004]. While Luchsinger et al showed neither dietary, supplemental, nor total intake of carotenes and vitamins C and E was associated with a decreased risk of AD [LUCHSINGER et al 2003].

3.5.2. Ginkgo biloba

Extract of the ginkgo leaves has been used in alternative medicine to treat circulatory problems, asthma, vertigo, fatigue, tinnitus, and cognitive disturbances. As a supplement, ginkgo biloba extract (GbE) is usually standardized to contain 24% ginkgo-flavone glycosides and 6% terpenoids [KELLEY and KNOPMAN 2008].

The positive effect of GbE on cognitive functions may be due to its properties of increasing blood supply by dilating blood vessels, reduction in blood viscosity, modification of neurotransmitter systems and also reduction in the density of oxygen free radicals [BIRKS and GRIMLEY 2009].

Several clinical trials have been conducted to investigate the benefit of GbE for dementia patients. A randomized placebo-controlled trial enrolled 309 subjects with AD or multi infarct dementia (MID), who received 120mg/d GbE for 52-weeks. Results showed a modest improvement, which is unlikely to be clinically relevant

[LE BARS et al 1997].

Another randomized controlled study with 513 AD patients as subjects used supplementation of 120mg and 240mg ginkgo extract daily for 6 months. There were no significant differences between the treatment and control groups. Since there was no adverse event reported in many trials, it seems that a high dose of GbE is well tolerated [SCHNEIDER et al 2005].

Overall, although some small and short-term clinical trials have shown modest improvement in cognitive function, large and well-designed clinical studies proved no efficacy of GbE supplementation for AD patients. No long-term data exists yet, and current evidence is inconsistent.

3.5.3. Curcumin

Data from epidemiological study show that India has the lowest prevalence of dementia in the world [VAS et al 2001]. Some scientists hypothesize a connection of this fact with the usage of spices in Indian diet. Curcumin, a polyphenol compound in curry powder turmeric, is thought to be the agent. In vivo, it passes the blood-brain barrier and has favorable properties such as antioxidant, anti-inflammatory, metal chelator, lowering cholesterol and anti-amyloid activity[81].

In animal experiment , mice fed with curcumin showed decreased total microgial activity, decreased cerebral levels of oxidized protein and interleukin -1ß[82]. Low dose (160ppm) of curcumin treatment seemed to decrease insoluble and soluble beta amyloid and plaque burden, while high dose (5000ppm) did not show these

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81 Anti amyloid activity would means to protect cells from beta amyloid cell death
82 Proinflammatory cytokine

effect [LIM et al 2001].

A clinical trial of curcumin therapy in AD patients is currently under way and preliminary results look promising [SIKORA et al 2010]. In general, curcumin is considered safe, even for a dose as high as 8mg/d, because of its poor bioavailability.

Overall, the data regarding supplementation of antioxidants in prevention and therapy of cognitive impairment are inconsistent. Mecocci and Polidori argue that low permeability of antioxidants through blood brain barrier may interfere with studies results. Moreover, correct dosage, choice of monotherapy or multiple antioxidants, and role of vascular factors should be considered in the studies [MECOCCI and POLIDORI 2011]. Positive results from observational studies may be due the synergic effect from combination between antioxidants with other nutrients in the diet, such as polyunsaturated fatty acids. Healthy diet rich in antioxidants compounds from fruits, vegetables, beverages and spices may be effective to prevent cognitive decline, if started early in life, before neurodegeneration occur [BREWER 2010].

3.5.4. Role of Metals in neuron degeneration

Some metals are suspected of playing a role in the pathogenesis of AD. In the brain of AD patients, metals such as aluminum, copper, iron, zinc are present in significant amounts compared to a healthy brain. They may act as catalysts for the production of free radicals [CHRISTEN 2000].
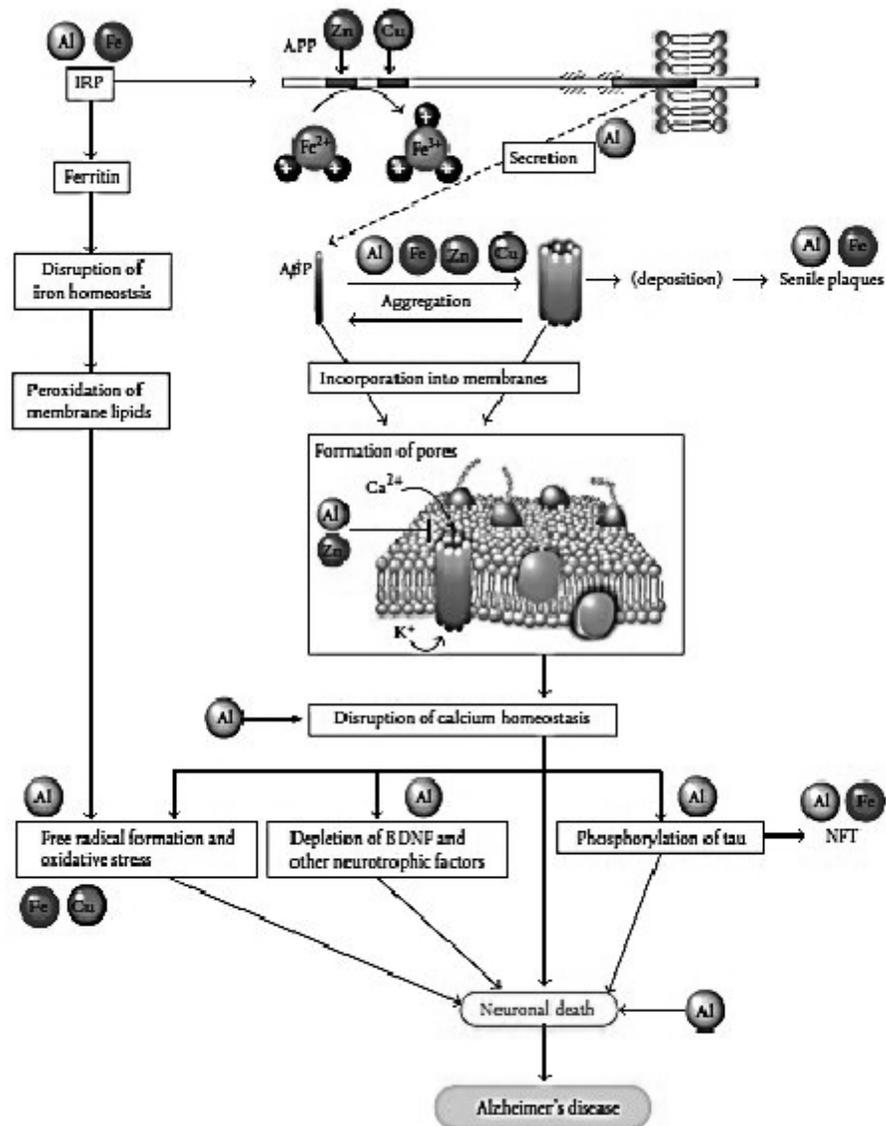
Illustration 8: Hypothesis of how aluminum, iron, copper and zinc may involved in the pathogenesis of Alzheimer's Disease [KAWAHARA 2011].

Questions arise on how and why these metals accumulate in the brain of AD, also how these metals cross the blood-brain barrier. Copper, iron and zinc are dietary minerals, the human body requires these trace elements in small quantities as co-factor for many enzymes. Perhaps a disturbance of the metals' homeostasis or absorption of detrimental metals with no known biological function may alter the balance and lead to neurological disorders [DUCE and BUSH 2010].

Studies from animal experiment and cell cultures has clarified the connection between metals and beta amyloid. From transition metals, beta amyloid can generate reactive oxygen species (ROS) radicals and deplete neuronal glutathione levels [STRAUSAK et al 2001]. Some studies investigate the effect of some chelating agents, which bind metals ion and prevent formation of ROS and therefore considered indirect antioxidants.

3.5.5. Aluminum

The connection between aluminum and AD was first proposed in 1965 by Klatzo et al. Their experiment reported, that the injection of aluminum salt into a rabbit's brain might degenerate neurofibrille and induce the formation of NFT [KLATZO et al 1965]. Autopsies showed that aluminum concentration is higher in the brain of AD patients, to be exact in the degenerating neurons in hippocampus, when compared to a normal healthy brain.

Symptoms similar to AD could be observed by residents of Camelford[83], who drank high levels[84] of aluminum sulphate from drinking water in 1988. Autopsy results

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83 In Camelford, UK, July 1988, aluminum sulphate accidentally contaminated drinking water supply, and caused adverse health effects.
84 Aluminum concentration found in water was 50-300 times greater than the acceptable limit concentration admissible by European Community.

from one resident who died due to a rare form of beta amyloid-angiopathy[85], showed a high level of aluminum in her brain up to 23 µg[86] per gram dry weight brain tissue [ALTMANN et al 1999]. Also in PAQUID cohort study, the prevalence of AD and cognitive decline were higher in residents with high level of aluminum intake [RONDEAU 2009].

Mechanism of how exactly aluminum affect neuronal death is still not yet fully understood, aluminum may increase oxidative stress and stimulate iron-induced lipid peroxidation, thus accelerate the pathological process [CHRISTEN 2000].

Aluminum's relation to other minerals is also interesting. Aluminum enters the brain through the blood brain barrier with transferrin-mediated transport [FARRAR et al 1990]. Silica is known to counteract aluminum absorption in the gastrointestinal tract and thus decrease its bioavailability [RONDEAU 2009].

3.5.6. Copper

Copper is suspected to cause or at least to play an important role in pathogenesis of Alzheimer's disease. Substances that are associated with AD; such as beta amyloid, APP, ß-secretase, tau protein; they all bind copper. Moreover, two risk factors for AD, apoE ε4 and homocystein also interact with copper [BREWER 2009].

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85 Beta amyloid angiopathy is a disease, in which deposits of amyloid befall walls of blood vessel of central nervous system.

86 A high concentration of aluminum is typical of dialysis-associated encephalopathies, a normal level of aluminum in brain is 0-2 micrograms per gram dry weight brain tissue.

Examination of AD patients shows that they have an elevated free copper level[87], which may be correlated negatively with cognitive performance in AD patients. [SQUITTY 2009]. The level of copper in the brain are affected by amyloid precursor protein (APP) expression, and the interaction between copper, APP and homocysteine can result in increased free radical generation and neurodegeneration [WHITE et al 2001].

High copper intake together with a diet high in saturated and trans fatty acids may be associated with cognitive decline according to one prospective study [MORRIS et al 2006]. The increased level of both cholesterol and copper seems to distress the brain. Although the mechanism is still unclear, changes in levels of superoxide dismutase, glutathione peroxidase and ceruloplasmin suggest that the combination of high cholesterol level and copper may promote oxidative stress, thus generate neuronal damage [BUSH et al 2003].

3.5.7. Iron

Iron is an essential metal in maintaining the function of the central nervous system, but like copper, iron may also induce the oxidative stress in neurons by forming free hydroxyl radicals. Two enzymatic indicators of cellular oxidative stress ; heme oxygenase (HO-1) and NADPH oxidase, seem to be activated in post mortem analysis of AD patients brain [TAKEDA et al 2000].

Accumulation of iron, transferrin and ferritin have been found in the brains of AD patients within specific brain regions, displaying selective vulnerability to neurodegeneration and their distribution matched the distribution of amyloid

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87 Copper is found in 2 forms in blood, one is bound to ceruloplasmin and other is rather loosely bound to albumin and small molecules in blood.

plaque and NFT [Bartzokis et al 2004] [SMITH et al 1997]. Evidence suggests that metabolism of iron is disturbed in brain of AD, perhaps due to genetic alterations specific to iron management protein[88]. Mutation in haemochromatosis[89] (HFE) protein has been linked with increased oxidative stress and severity of AD [BRAAK et al 1993] [PULLIAM et al 2003]. Its expression is induces in cells associated with neuritic plaques [CONNOR et al 2001]. Experiment in vitro shows, that iron is required for beta amyloid toxicity. The deletion of iron or inclusion of iron chelator reduce toxicity of beta amyloid [ROTTKAMP et al 2001], suggesting that iron may play an important role in the pathology of neurodegenerative diseases [MANDEL et al 2007].

3.5.8. Zinc

In the brain, zinc is bound to metalloprotein of neurons and glial cells. Its function is not yet fully understood, but it could act as a neurotransmitter or neuromodulator. Zinc may participate in glutamate storage, release and uptake , and in modulation of glutamatergic receptors [TAKEDA 2000].

In animal experiments, high zinc concentration is shown to be neurotoxic. Zinc binds to beta amyloid and the bond between zinc and APP may change functional features of APP and may promote aggregation of beta amyloid protein [CHRISTEN 2000]. The mechanism may be through changes in the key proteins, such as zinc transporter protein ZnT-6, responsible for the maintenance of zinc homeostasis in the early development of Alzheimer's disease [FERRY and ROUSSEL 2011]. Studies also found, that total tissue zinc is increased in several

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88 Iron-binding protein and iron regulatory protein (IRPs) such as transferrin, ferritin, IRP1 and IRP2, are involved in iron homeostasis and storage.

89 Haemochromatosis is an iron overload condition, mostly hereditary.

brain regions of post mortem AD patients, suggesting that abnormal zinc metabolism may contribute to the development of AD [CUAJUNGCO and FAGET 2003].

Zinc seems to have detrimental effect if consumed both in excessive and deficient dose. Deficiency of zinc could induce decreased taste perception and decreased desaturase activity, which may impaired body accumulation of polyunsaturated fatty acids [CUNNANE and YANG 1995][WAUBEN et al 1999].

In connection with cognitive function, Ortega et al found a positive correlation between zinc and cognitive tests MMSE (Mini-Mental State Examination) and PSMQ (Pfeiffer's Mental Status Questionnaire) in 260 Spanish subjects [ORTEGA et al 1997]. Although further researchs is needed to confirm the relation between zinc and neurodegeneration, adequate intake of zinc seems to be an important aspect to maintain good cognitive function, especially since elderly persons are at risk for zinc deficiency.

3.5.9. Heavy metals

Pollutants such as lead and mercury are also suspected of playing a role in the neuropathology of dementia. Heavy metals may be involved in the pathological process of AD, such as mitochondrial dysfunction, oxidative stress, deregulation of protein turnover and brain inflammation. Early exposure in life or accumulation during prolonged period may present delayed toxic effect later in older age [MONET-TSCHUDI 2006].

Methylmercury, a non-toxic and the most common form of mercury in the environment, may become neurotoxic under pro-oxidant conditions. As shown in

cell culture, mercury and lead may induce glial cell reactivity[90], increase the expression of the amyloid precursor protein and stimulate the formation of insoluble beta amyloid in brain [MONET-TSCHUDI 2006] .

3.6. Caloric Restriction

Luchsinger et al showed that high total calorie and fat intake in individuals homozygous or heterozygous for ApoE ε4 allele is associated with higher risk of AD [LUCHSINGER et al 2002]. On the other hand, calorie restriction[91] (CR) without malnutrition has been demonstrated to slow the ageing process and extend life span in animal experiment. Dietary restriction may induce mild cellular stress response in neurons, as its effects on energy availability. Neurons respond to this stress by increasing the production of neutrophic factors protein chaperones and antiapoptotic proteins; these protein support cellular resistance to neuron degeneration and may stimulate neurogenesis and synaptic plasticity [MATTSON 2003]. Moreover, caloric restriction is also found to decrease homocysteine and insulin[92] levels, which would be beneficial to prevent age-related damage to cerebral blood vessels.

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90 Reactivity of glial cell indicates brain inflammation.
91 Caloric restriction is defined as a reduction of caloric intake (approximately 20%) compared to ad libitum feeding without malnutrition.
92 A high insulin level is associated with a decreased in cognitive and memory function.
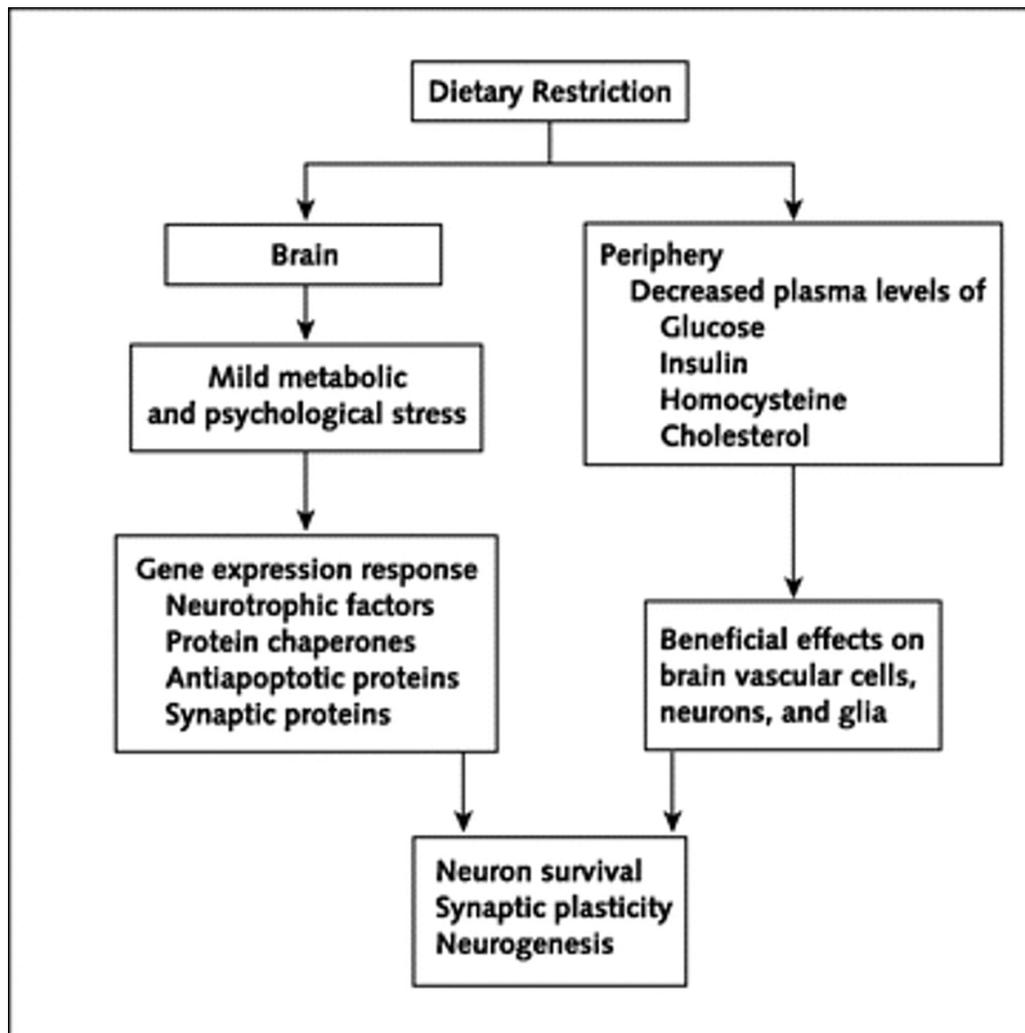
Illustration 9: Neuroprotective effect of dietary restriction [MATTSON 2003].

The condition of CR may modulate fat and carbohydrate metabolism, attenuate oxidative damage and activate a stress-induced hormetic response that mediates improved vitality and disease resistance [BOGAN and BRENNER 2008]. In vitro, when placed in sublethal stress condition, cell increases the metabolism of NAD^+ in a manner that favors sirtuin[93] (SIRT1) activity. CR effect of increased lifespan did not occur in sirtuins knockout mice, suggesting that sirtuins is necessary for

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93 There are 7 family members of sirtuins identified in human;SIRT1 to SIRT7.

mediating effect of CR [CHEN et al 2005]. In CR-treated mice, SIRT1 activation has been proved to reduce Alzheimer's neuropathology [QIN et al 2006].

In another experiment, a 30% CR in mice model of AD resulted in reduced contents of Aß1-40 and Aß1-42 peptides and elevation of α-secretase activity, which subsequently may lower amyloid pathology [WANG et al 2005]. In addition, there was also a reduction of reactive oxygen species and suppression of Monoamine oxidase-B[94].

To date, intervention studies in human subjects are few, but available data seems to support the hypothesis that CR may be beneficial to prevent cognitive deterioration. One clinical trial with healthy elderly observed improvement of verbal memory after 3 months of 30% caloric reduction. Mechanism underlying this effect is perhaps correlated with decreased fasting plasma levels of insulin, reduced inflammatory activity and high sensitive C-reactive protein [WITTE et al 2009].

Interestingly, intermittent fasting[95] seem to result in same physiological benefits as CR. In mice, both methods result in reduced serum glucose, improved insulin sensitivity and increased resistance of neurons in the brain to excitotoxic stress [ANSON et al 2003].

Although calorie restriction is promising in prevention of dementia, it is still too early to consider its implementation in human. Questions arise such as the right dose at which calorie restriction would not cause adverse effects or the right time[96] to begin CR.

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94 Monoamine oxidase is an enzyme that promote oxidative stress in brain.
95 In this experiment, intermittent fasting-mice are deprived of food for 24 hours every other day.
96 In animal studies, CR should be started early in life, it has no value in prolonging life if it is begun too late.

If the dietary restriction theory suggests the reduction of calorie intake to prevent neurodegeneration, on the other hand, dementia patients are usually encouraged to eat more. They usually lose weight at initial onset, and this condition will get worse during the course of disease. Malnutrition is the main nutritional issue during the course of AD, and CR may bring more risk than benefit in this group.

3.7. Dietary patterns associated with decreased risk of AD

Most knowledge about the development of dementia is based on the role of nutrients rather than that of foods. But since individuals do not consume nutrients in isolation and meals consist of complex combination of nutrients, implementation of this knowledge into the diet may be difficult. An alternative approach is to assess dietary patterns and its association with neurodegenerative diseases.

Results from a prospective cohort study with 2148 community-based elderly subjects showed, that dietary pattern characterized by high intake of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables and low intake of high-fat dairy, red meat , organ meat and butter, are strongly associated with lower risk of AD. The diet in this study is rich in ω-3 PUFA, ω-6 PUFA, vitamin E, and folate, but low in saturated fatty acids and vitamin B_{12} [GU et al 2010].

One of the diet emphasizing foods rather than nutrients is Mediterranean diet, which has been associated with reduced risk for cardiovascular mortality and cancer incidence [SOFI et al 2008]. The relationship between Mediterranean diet and brain health has only recently explored.

Mediterranean diet

Mediterranean diet is characterized by high intakes of vegetables, fruit and nuts, legumes, cereals, fish, and monounsaturated fatty acids (MUFA); relatively low intakes of meats, dairy products; and moderate alcohol consumption [PANZA et al 2007]. High consumption of extra-virgin olive oil is the hallmark of this diet. High level of MUFA and polyphenolic compounds in extra-virgin olive oil is postulated to protect against cognitive decline [SOLFRIZZI et al 2006].

Since the diet is varying considerably across Mediterranean countries, "Mediterranean Diet Score" has been developed. The score consists of nine food groups characterizing the traditional Mediterranean diet (vegetables, fruits, legumes, cereals, the ratio of monounsaturated-to-saturated fatty acid, alcohol and fish presumed to be beneficial; while meat and dairy products presumed to be detrimental), where a value of 0 or 1 is assigned to each group. Higher score indicating closer adherence to Mediterranean diet [FÉART et al 2010].

To date, only two prospective studies have investigated the relation between Mediterranean diet and cognitive function [FÉART et al 2010]. Scarmeas et al reported, using data from the Washington Heights-Inwood Columbia Aging Project (WHICAP), a higher adherence to Mediterranean diet is associated with lower incidence of dementia and AD [SCARMEAS et al 2006]. Moreover, according to the same author, adherence to Mediterranean diet may lower the risk of MCI patients to develop AD [FÉART et al 2010] [SCARMEAS et al 2009].

Another prospective study used data from Three-City (3C) study, concluded that higher adherence of Mediterranean diet was associated with better global cognitive performances and episodic memory over time, but there was no association between Mediterranean diet's adherence and risk of dementia [FÉART

et al 2009].

At first, risk reduction of AD is thought to be mediated by the diet-induced beneficial vascular risk factors, but significant association remains in both studies after adjusted to vascular variables [FÉART et al 2009] [SCARMEAS et al 2006]. This may be explained by the content of antioxidants and anti-inflammatory nutrients in the diet [FÉART et al 2010].

Féart et al suggested , the Mediterranean diet would only be efficient and beneficial for cognitive function, if implemented at least 5 years before the clinical diagnosis of dementia. After that, the neurodegeneration may be too advanced to be reversed by diet [FÉART et al 2010].

Perhaps it may not direct effect of specific diet or nutrients that provide the protection but a healthy diet and moderate lifestyle in general that protects from cognitive decline [PANZA et al 2007].

Healthy diet, moderate lifestyle and risk of dementia

Eating in moderation like in Mediterranean diet has been proved to benefit cognition, since dietary excess may influence the development of age-related disease. One study compared dietary habits between AD and VaD patients with a healthy control group. Results showed that AD and VaD patients had a higher energy intake. Major sources of energy were grains and animal fats for the AD group, while VaD patients consumed mostly grains. Compared to the healthy group, excess intake of ω-6 PUFA and deficiencies of ω-3 PUFA, antioxidants, vitamin C, carotene and the vitamin B group were observed [OTSUKA et al 2002]. Another study by Luchsinger et al confirmed the result, that high calorie and fat intake may be associated with a higher risk of AD, especially for individuals with

ApoE ε4 gene [LUCHSINGER et al 2003].

Another study investigating the effect of low carbohydrate diet in elderly with mild cognitive impairment (MCI). 23 subjects were assigned for either high or very low carbohydrate for 6 weeks. In the low carbohydrate group, improvement in memory performance, reduction in weight, reduced waist circumference, as well as reduced fasting glucose and fasting insulin were observed [KRIKORIAN et al 2010].

Small et al conducted a 14-day healthy longevity lifestyle program for MCI patients, and found that word fluency and activity of some brain area were beneficially affected after the intervention. The diet plan was high in antioxidant fruits and vegetables, ω-3 PUFA, low glycemic index carbohydrates. The program consist not only of nutritional intervention, but also exercise and cardiovascular conditioning to reduce stress [SMALL et al 2006].

In conclusion, food choice and dietary habits together with lifestyle factors are likely contribute to the development of neurodegenerative diseases. Antioxidant compounds, B-vitamins, ω-3 fatty acids, low caloric and low glycemic index carbohydrates diets, have been investigated concerning their involvement in the pathology of dementia and AD with contradicting results. However, recent evidence seems to confirm the role of nutrition. As a modifiable factor, if implemented early in life, a healthy diet may present a potential preventive approach against dementia.

3.8. Researchs limitations

It is difficult to design an experiment to study the connection between one specific substance and the development of cognitive impairment, since the pathology of dementia in humans may take a long time to develop. Moreover, many factors interfere with dietary intake; such as genetic, lifestyle and synergistic or antagonistic effects between nutrients; their interactions may contribute to deposition of plaque and NFT.

The confirmed relationship of nutrients to dementia is mostly based on cell cultures, animal experiments and epidemiological studies. Clinical trials available today rarely deliver positive result, bias from selection methods (differences in baseline status of the subject persons), dose and forms of nutritional intervention used (nutrients from supplementation or diet), assessment methods, duration of study etc. make it difficult to interpret the results. Issues and limitations to each of these study methods should be considered in data interpretation.

The animal testing has its limitation in its inability to deliver exact data, since not all animals naturally develop tangles and plaques – therefore transgenic[97] animal models are designed through genetic, biochemical, or dietary manipulations to develop AD. Fruit fly, mouse, rabbit, dog, primate species and mice are usually used. Difference in gene polymorphisms may cause these animals to produce less enzymes that support the production of plaques and tangles. This may make the identification of true risk factors difficult, e.g. to make transgenic mice overexpressing mutant APP to develop amyloid plaques, endogenous level of APP have to be make at least 8-fold, while human already develop AD with 50% increase in APP [DUFF and SULEMAN 2004].

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97 Transgenic animals are animals with genes knocked out, inserted or imported from human genes

Another example is neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), that causes parkinsonism in humans. Rodents are much less susceptible to the adverse effect of MPTP. Although there are cell death found in the substantia nigra, but parkinsonian symptoms do not appear like in human. It is believed that the lower levels of monoaminooxidase-B (MAO-B) in the rodent may be responsible for this [LANGSTON 2002].

Although results from animal studies may be unreliable, in AD research it is still necessary, as it is cheaper and less time consuming than other experimental methods. Further, it is an efficient method to investigate biological mechanisms involved in the pathology of neurodegenerative diseases.

4. Malnutrition in dementia

A good nutritional status is beneficial in supporting therapy, to avoid further complication and ensure quality of life for patients with dementia. The negative impact of malnutrition will bring further complications such as infections, faster loss of independence, and a higher mortality rate. But often, it is difficult to maintain a good nutritional status, since people with dementia in all stages lose weight, even in the early stages before diagnosis.

All studies agree that malnutrition brings about adverse health effects. Increased vulnerability to infection, delayed wound healing, a decreased rate of drug metabolism, impairment of physical and cognitive function, and progressive clinical deterioration are some of the complications. Furthermore, malnutrition in the elderly seems to be more difficult to correct than in younger adults [FIATARONE et al 1994].

Even in healthy elderly people, energy regulation may be impaired. Unlike young adults, elderly people tend not to adjust their food intake after periods of over- or underfeeding, which makes them more prone to acquiring a negative energy balance [ROLLS et al 1995].

Overall, undernourishment results in increased morbidity and mortality in the elderly together with a decreased quality of life [JORDAN et al 1999]. The consequences of malnutrition are summarized in table10.

Complications:
- – Pressure sore formation
- – Compromised immune functions
- – muscle atrophy
- – Increased rate of infections
- – Longer recuperation periods
- – Loss of independence
- – Decreased mobility with increased risk of falls and fractures
- – Impairment of the immune system and increased susceptibility to infection
- – Increased the risk of institutionalization hospitalizations
- – Delayed rehabilitation after acute illnesses
- – Reduction in quality of life
- – Increased mortality

Table 10: Complications of malnutrition in elderly [HIRSCH 2004]

4.1. Definition of malnutrition in context of elderly with dementia

The word malnutrition may has several indications, such as:

1. undernutrition caused by inadequate food intake

2. overnutrition, resulting from excessive food intake

3. specific nutrient deficiencies

4. imbalance because of disproportionate intake

[KELLER 1993]

In terms of older people, malnutrition is further characterised with :

1. inadequate food intake and

2. protein caloric malnutrition (PCM) or protein energy malnutrition (PEM)

[CHEN et al 2001]

Insufficient intake of essential nutrients is assumed to deplete nutrients storage
and then occur a negative energy balance between quantity (and quality) of food

intake and energy expenditure.

Loss of lean body mass and fat tissue is the main characteristic of PCM, which clinically is divided into 3 types: marasmus, kwashiorkor, or a mixture of both. In the elderly, the latter type is most present.

	Marasmus	Kwashiorkor
Clinical causes	Insufficient calorie intake	Insufficient protein intake during stress/illness
Clinical features	Starved appearance Weight <80% standard for height Triceps skin fold <3mm Mid-arm muscle circumference <15cm	Well-nourished appearance easy hair pluckability oedema
Laboratory data	Creatinine-height index <60% norm	Albumin <3.5/3.0 g/dL
Time to develop	months	weeks

Table 11: Types of Protein Calories Malnutrition [CHEN et al 2001]

Weight loss in AD patients is more prominent than in the healthy elderly. In one study, the BMI in subjects without Alzheimer's disease decrease by an average of 0.14 a year, compared with 0.52 a year in similar subjects with probable Alzheimer's disease, as seen in Figure 3. The severity of Alzheimer's disease do not seem to modify weight loss: the body mass index decreased by 0.59 a year in subjects with mild disease and by 0.47 in those with advanced disease. [CRONIN-STUBBS et al 1997]

Weight loss in the development of AD is divided into 2 types. The first type is a progressive loss, which occurs in around one third of AD patients, in this case body weight is reduced by about 4% in 1 year. The second is a severe type,

occuring in circa 10% of patients, whose weight was reduced by over 5 kg in 6 months [GUÉRIN et al 2005].

Illustration 10: Estimated weight loss for women with and without AD. The graphic below is adjusted for age and sex. [CRONIN-STUBBS et al 1997].

Unadjusted data

Mean body mass index

○——○ Subjects without Alzheimer's disease
●——● Subjects with Alzheimer's disease

n=111
n=32
n=237
n=119
n=75
n=38
n=156
n=33
n=32
n=18

Adjusted data

Body mass index

○——○ Average woman without Alzheimer's disease
●——● Average woman with Alzheimer's disease

Entry   1   2   3   4

Year of observation
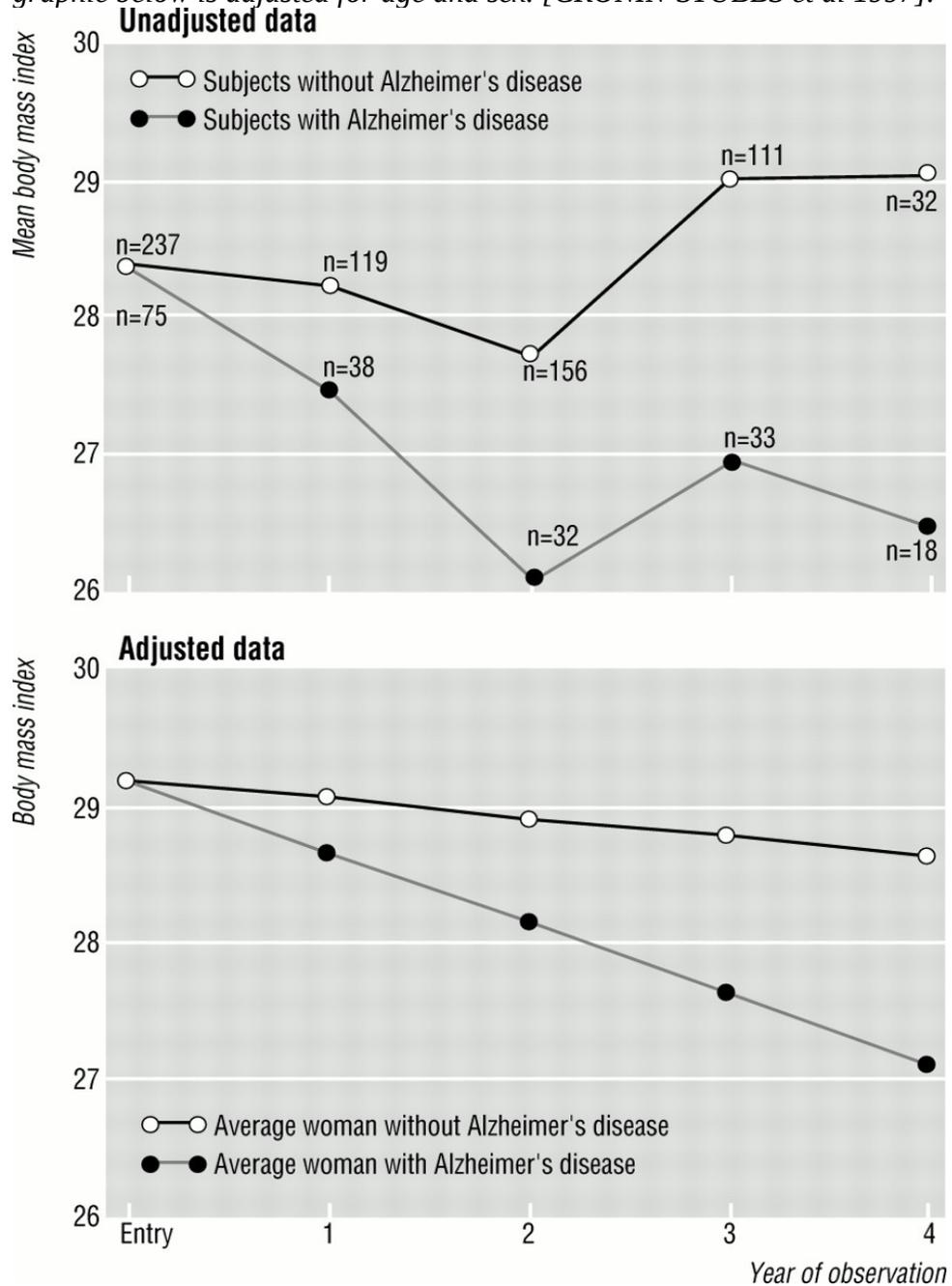
4.2. Epidemiology

In literature reviews, the prevalence of malnutrition in the elderly with dementia varied because of differences in methods applied and the type of settings in which the study was conducted. In USA and Canada figures range from 10% to 85% [THOMAS 1999].

In Germany, according to *Altenbericht 2004,* 25 % of people with dementia in nursing homes are malnourished. Figures from Austria are similar [MESSER et al 2005].

The fact that malnutrition is a continuous phenomenon makes it difficult to measure. Assessment of insufficient dietary intake may help evaluate the risk of malnutrition, whereas nutritional status reveals the current state an elderly person reaches after being undernourished.

4.3. Risk of malnutrition in elderly people

Physiological changes in old age include increased body fat, reduction in bone density, loss of muscle mass, total body water and lean body mass. These changes in body composition lead to a decreased[98] basal metabolic rate and usually alteration in body mass. Humans' body mass tend to increase from adulthood to 70-75 years old, afterwards decrease [RITZ 2001].

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98 Reduction of basal metabolic rate is around 2% per decade [ELMADFA and LEITZMANN 2004].

Fat-free mass tend to be lower in AD patients than healthy subjects, while there is no difference in fat mass between two groups. Daily energy expenditure is 14% lower, due to lower resting energy expenditure and physical activity [POEHLMAN et al 1997].

Comparing body compositions of Parkinson's patients with healthy elderly, both fat mass and fat-free mass does not differ between groups, therefore resting energy expenditure remain the same. Daily energy expenditure is around 15% lower in Parkinson's group due to lower physical activity [TOTH et al 1997].

Changes	cause
Reduced energy expenditure	Decline in BMR reduced physical activity decrease in active muscle mass (increased body weight)
Digestion slowing down	Decrease in saliva production decline in gastric secretion reduced fat and calcium resorption reduced carbohydrate tolerance
Decrease adaptation capability	Decreased odor and taste perception decreased thirst increased chewing difficulties chronic illness

Table 12: Changes in body metabolism in older age [ELMADFA and LEITZMANN 2004]

Food intake is decreased in aging and make elderly people more prone to develop malnutrition. In one observational study, older adults make different food choices, they consume less dense sweets and fast food, but more energy-dilute grains, vegetables and fruit [DREWNOWSKI and SCHULTZ 2001]. Reduction in dietary variety is also observed, and this may be related to a decreased in overall energy intake [KWON et al 2006].

Weight loss is often observed even if subjects still have satisfactory energy intake. Some studies assume the atrophy of the internal temporal cortex or the effect of the ApoE ε4 allele in the development of AD may play a role in weight regulation [VANHANEN et al 2001].

Malnutrition in elderly may be caused by physiological , pathological, psychological and social factors (Table 13).

Physiologic	Pathologic	Sociological	Psychologic
Decreased sensory function (smell and taste)	Poor dentition	Ability to buy and prepare food	Depression
Dysregulation of satiation	Dysphagia, swallowing problem	Financial issue : poverty	Anxiety
Delayed gastric emptying	Chronic diseases (cancer, diabetes, thyroid, etc.)	Impaired ADL skills	Loneliness
Decreased gastric acid	Medication	Lack of interaction with others at mealtime	Emotionally stressful life events
Decreased lean body mass	Alcoholism		Grief
Decreased salivary flow	Dementia		

Table 13: Risk factors for malnourishment in elderly [MORLEY 2002]

Feelings of satiety and hunger are modulated by peripheral signals. Cholecytokinin (CCK)[99] and Peptide YY (PYY), as short-term postprandial[100] signals, have been shown to be stronger in the elderly than in younger adults. Further, fasting leptin[101] as well as plasma fasting and postprandial insulin are also higher in elderly

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99 CCK and PYY are involved in the regulation of satiety and hunger.
100 Postprandial means after a meal.
101 Leptin is a hormone that decrease appetite and is involved in long term satiety.

subjects, which may result in prolonged satiety and inhibition of hunger. High insulin levels are positively associated with satiety [DI FRANCESCO et al 2006].

Presence of a chronic disease in old age may increase the risk of malnutrition. In cancer, chronic infection and cardiac disease patients, weight loss mechanism involved cytokine mediated cachexia[102] syndrome. Proinflammatory cytokines such as TNF-α, IL-1, IL-6 and IFN-γ may alter central and peripheral neurohormonal signals that control appetite. Moreover, cancer cachexia is associated with changes in carbohydrates, lipid and protein metabolism [BENNANI-BAITI and DAVIS 2008]. But in case of patients dementia, weight loss does not seem to be cytokine-mediated [REGNARD et al 2010].

Partial loss of optimal oral health and sensory perception may influence appetite and the pleasure of eating. Poorly fitting dentures , mouth pain, dry mouth, and other symptoms that make eating uncomfortable, may increase the risk of malnutrition in elderly. Chewing and swallowing difficulties also limit food selection. Oral dysphagia is noticeable as absent or continuous chewing, whereas pharyngeal dyphagia showed by delayed swallowing initiation, multiple swallows and aspiration, which could lead to pneumonia [LANGMORE et al 2007] .

Some medication could also interfere with vitamin absorption[103] , affect oral health, decrease salivary flow, cause atrophy of mucus membranes and loss of taste buds [MARTIN 1999].

Another problem is the deterioration of sensory perception. An elevated taste threshold is observed if more drugs are consumed. The table below shows the

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102Cachexia is a progressive wasting syndrome, characterized by a loss of fat and lean body mass (LBM). On the contrary, in starvation LBM is preserved.

103Trimethoprim and phenytoin interfere with folate; Cholestyramine, mineral oil and neomycin interfere with vitamin A, Hydralazine interfere with vitamin B6; INH increase urinary excretion of vitamin B6 : [GERSHMAN and McCULLOUGH 2002].

average detection threshold for elderly taking 3-4 medications compared to younger adults.

	Salty	Acid	Sweet	Bitter
Times higher	11,6	4,3	2,7	7

Table 14: Detection threshold for elderly , who take medications, in comparison to young adult [SCHIFFMAN 1993].

In some studies, the loss of olfactory function is associated with a loss of appetite and weight. Smell loss will be perceived as taste loss according to one study by the University of Pennsylvania Test and Smell Center. From 750 subjects who complained about taste loss, only about 4% had measurable taste deterioration, while 71% had in fact olfactory impairment [DEEMS et al 1991].

Partial loss of vision and hearing may bring difficulties in shopping and preparing food. Moreover, it may also affect social contact, reduce competence for activities of daily living, increase the risk of falls and fractures, it also may result in eventual stress and depression.

Psychological and social factors should not be underestimated in cases of the elderly with dementia. Depression, loneliness, anxiety and other dysphorie can result in refusal to eat. Changes in older life like retirement, loss of partner or friends, loneliness, financial problems, dependency, chronic illness, moving to a nursing home, forming new attachment and adapting to a new social life may increase stress and the risk of depression. It is often reported that institutionalized elderly try to run away from care homes, it describes more or less their mental state and it is sure difficult to expect a good nutritional status in such condition. Indeed, change of living arrangements is one of the risk factors for severe weight loss [GUÉRIN et al 2005].

Basically, conditions of living for elderly can be sort as follows:

Housing options	Food supply
Staying in one's own home	Cooking
Nursing home	Nursing home catering
Hospital	Hospital catering

Table 15: Conditions of living for elderly with dementia

After onset of dementia, the deterioration of cognitive function makes it difficult to prepare and organize meals. Living alone for the frail elderly is unsafe and over time people with dementia become dependent on their caretaker. In Germany, around 60% of people with dementia are cared for by a relative [Germany's 4th Ageing Report 2002]. Since they need a high level of maintenance and the demands of continuous care become increasingly difficult, both physically and psychologically, dementia is the main reason for moving to a nursing home.

4.4. Assessment tools

Considering the many factors that may cause undernourishment, nutritional assessment is mandatory in order to recognise malnutrition early and initiate nutritional therapy. Three measurement systems applied to identify malnutrition in the elderly are assessment of dietary intake, biochemical indices and anthropometrical data.

Dietary intake	<75% of RDA in >=3 key nutrients <2/3 of RDA in >4 nutrients <50% of calculated maintenance energy requirement
Biochemical indices	Serum albumin <30mg/dL Serum transferrin <20g/L Total lymphocyte count <1.5 cells/mm
Anthropometrics	BMI <5 percentile BMI <20 Mid-arm circumference <5 percentile Arm muscle circumference <5 percentile Triceps skinfold <5 percentile Weight <75% standard weight for height Weight <80 percentile standard weight for height <90 percentile standard weight for height Loss of >5% of weight in 6 months

Table 16: Measurement system to identify malnutrition [CHEN et al 2001]

Other important parameters are weight tracking, nutritional history, medical history, observation of eating behavior and laboratory parameters (albumin, protein, fatty acid, cholesterol, electrolyte, trace minerals, vitamin B).

One measurement system alone may not be sufficient to recognize a case of malnutrition. Serum albumin, for example, although many physicians consider the measurement of serum albumin to be an adequate assessment of nutritional status, is however, in hospitalized patients, influenced by many other factors, that may disturb the result [COVINSKY et al 2002].

Many nutritional screening and assessment tools[104] have been developed in recent years containing either clinical, biochemical or anthropometric tests, such as:
• Mini Nutritional Assessment (MNA)
• Edinburgh Feeding Evaluation in Dementia (EdFED) -Scale

104Screening tools aims to identify those at risk of developing malnourishment, whereas assessment tools is performed more extensively to define the state of elderly person.

• Resident Assessment Instrument – Home Care (RAI HC 2.0)

• Nutritional Form for the elderly (NUFFE)

• Subjective Global Assessment (SGA)

• Nutritional Screening Initiative (NSI)

• Senior in the Community: Risk Evaluation for Eating and Nutrition (SCREEN)

• Nutrition and drinking history (Ess- Trinkbiografie)

Mini Nutritional Assessment (MNA)

MNA is widely used in many countries and usually assess upon admission to nursing home or hospital. Questions cover general health, dietary and anthropometric assessment, subjective and global evaluation, which consists of background situational living, medication, psychological condition and diseases [10] . Benefits included a reliable , very simple non-invasive, easy to administer, patient-friendly, non-expensive, very sensitive, highly specific, reliable and validated screening instrument for malnutrition in the elderly [VAN NES et al 2001] . The MNA scores were found to be significantly correlated with nutritional intake [VELLAS et al 2000], though the test intended to assess general nutritional conditions of elderly and therefore might be inadequate for people with dementia.

Edinburgh Feeding Evaluation in Dementia (EdFED) – Questionnaires[105]

One of few assessment tools specialized in nutritional matter of people in late -stage dementia is the Edinburgh Feeding in Dementia Questionnaires. This assessment questions the frequency of certain behaviors which may indicate progressive decline, andthus could be used to measure eating and feeding difficulties in elderly with dementia.

The test consists of 11 questions, the first four reflects behavior which indicates how far assistance is required during mealtimes such as how often the patient

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105[Watson and Dreary 1997]

needs close supervision, physical help, spills food and leaves food on the plate. Another 6 questions try to identify functional decline and asks the frequency of refusing to eat, turning head away, spitting out food, leaving mouth open and refusing to swallow. The last question brings out an overall rating of the support needed, with three available options :

• supportive-educative assistance, e.g. ihelp in plate setup, refocusing, but still able to feed himself/herself

• partly compensatory assistance, is if the patient is involved with the meal but physical assistance is needed

• wholly compensatory assistance, namely hand-feeding

This observational test should be administered during meal time and inconspicuously. The observer will record how often some distinct characteristic behavior appears during a meal. This will be quantified in a scoring system; 0 points for when the characteristic is never observed, 1 for sometimes and 2 for often. A higher score means greater disorder.

Although this test not a diagnostic tool, it is a valuable and helpful instrument to observe behavior, determine needs and make an effective intervention plan [STOCKDELL et al 2008].

Others assessment tools, such as food biography is sometimes necessary before acceptance in nursing homes. That way, it is easier to find out about favorite foods and track down personal history regarding eating behavior, in case malnutrition emerges.

Most assessment tools available today, measure objective symptoms and not what patients want or need regarding food intake. Anideal screening test is difficult to obtain. Some issues with these tests are, that [YITSHAL and BERNER 2003] :

- parameters of test often do not reflect physiological, physical, cognitive and emotional function

- nutritional assessment using objective markers is more complicated in older subjects because metabolic changes affect some of the routine biochemical test results

- the reference values of the anthropometric measures are not always age-adjusted

- functional impairment may occur at a subclinical level and precede a measurable alteration in body composition

In nursing homes facilities, effective weight tracking and tracking food/fluid intake systems may support the identification of significant weight loss of residents. Furthermore, screening tools provide individual informations and help to determine intervention plan.

4.5. Prevention of malnutrition

Proper nutritional care can reduce the prevalence of malnutrition. In one study, body weight of 33 dementia residents, who are being treated in special care units (SCU), can be maintained through comprehensive assessment and intervention, including enchanced menu designed to be individualized for ambulatory people with dementia [KELLER et al 2003]

A nutritional planning programme should consider not only dietary symptoms, but also personality and enviromental factors, such as declining cognitive abilities and the many factors that are involved in mealtime arrangements. Often nutritional disorders are not necessarily consequence of dementia, but merely a reaction of stress.

The table below shows some ideas to support good nutrition and in considering eating plan for elderly with dementia.

Review regularly	– Dental health – Medications intake – Food and fluid intake – Observation of eating habits – Documentation of food intake – Regular weight control
Food/ dietary factor consideration	– Energy-rich diet – Quality control of food – Food preparation : make food appealing by experimenting with spices and recipes. – Take into consideration patients wishes – If necessary : meal supplementation or meal replacement – Special diet for elderly with chewing and swallowing disorders
Consider how to eat, encourage to eat independently	– Frequent small meals – Eat independently or being feed, Provide specific tools to dinner – tools to facilitate independent eating, – Personal ritual, about how to eat, etc – don't pay much attention to manners and cleanliness /tidiness
Arrange a comfortable environment	– Avoid disturbance in eating environment, dining atmosphere – Creating a pleasant atmosphere, make it an social events – take enough time to eat, let eating be an pleasant experience
Other considerations	– Possibilities to encourage eating : stimulate appetite – Individual supervision during meals – Upright posture, encourage physical activity – helping and supporting at meal time, but encourage to self-reliance

Table 17: Intervention to prevent malnutrition in elderly with dementia [HIRSCH 2004]

In some literature, tube feeding is considered a prevention measure, whereas will be explained in chapter 6, that tube feeding may not be favorable for elderly in the advanced stage of dementia.

4.6. Dehydration and fluid intake

Along with the subsiding feeling of hunger, the feeling of thirst also declines in old age, making the risk of suffering from dehydration greater. Some old habits, such as a fear of a visit to the toilet at night, the fear of incontinence, or the desire to reduce the amount of urine in case of incontinence, could worsen the condition.

Changes in old age, that may influence fluid intake:
- reduced body water
- reduced thirst sensation, thus reduced daily water intake
- difficulty of obtaining liquid
- increased diuresis
- inadequate compensation for extra-losses (e.g. In summer)
- diuretics medication

Table 18: Influence of age on fluid intake [HIRSCH 2004]

Minimum fluid recommendations for the elderly is 1,5-2L daily. Changes in body weight, disorientation, dizziness, weakness, apathy, unconsciousness, kidney and (circulatory) failure are some complications as that impact from dehydration, which may lead to severe health conditions.

Intravenous hydration and subcutaneous hydration have been seen as alternative methods of maintaining fluid intake if patients seem to suffer from dehydration. Administration of intravenous fluid requires hospitalization, and the elderly with dementia may feel disturbed or uncomfortable with equipment attached, it is

therefore not a method that can be applied at any time.

Meanwhile, subcutaneous hydration, also called *hypodermoclysis* is still not common in geriatrics practice, although the instrument is quite easy to install, relatively safe, simple, cost effective and has little side effect if applied properly [HIRSCH 2004]. Although inadequate to correct severe dehydration and electrolyte imbalance, it may provide appropriate treatment if patients are not in hospital and like to move steadily. Indication for these methods are mild to moderate dehydration, also in the case of dysphagia. It is not recommended in acute situations namely severe dehydration and to patients with severe heart failure, it is also not for patients with a history of renal failure, coagulation and bleeding disorders.

A butterfly needle is placed and fluid containing 0,9% sodium chloride injected subcutaneously, about 500ml given over 8-12 hours, or 1000ml-2000ml over 24 hours.

To date, there is not enough evidence about the benefits and disadvantages of these two methods for the elderly with dementia, thus the decision is normally taken by patients or family members by considering preference or convenience and the purpose of treatment care.

Although oral drinking does not guaranteed sufficient fluid intake, for some elderly with terminal illness, it is still the best way to maintain comfort and quality of life. Simple measures, such as giving numbers to glasses in order to observe how many glasses are being drunk during the day can bring major changes.

4.7. Eating problems

Although eating problems are frequently marked as a complication at the late stage, changes in eating behavior or swallowing may occur early in progression of disease [PRIEFER and ROBBINS 1997). Priefer found a difference in swallowing patterns and eating behavior from people with mild-AD compared to the healthy elderly. People with AD significantly needed more assistance or "act-initiation" during mealtime, and in general have a longer swallow duration.

But it seems that the emergence of eating problems in dementia depends on which area of the brain is affected. One study compared eating problems in AD and FTD, it concludes, that change in eating behavior was more common in FTD than AD subjects [IKEDA et al 2002]. Disturbance in the right side of orbitofrontal-insular-striatal, which is common in FTD patients, is associated with overeating [WOOLLEY et al 2007]. Another study also compare eating disorders between FTD and AD, found that FTD patients tend to show disturbance of satiation, inappropriate way of taking food, and unfitting responses when food was not available [MENDEZ et al 2008].

Persistence of malnutrition in the elderly with dementia raises a question whether weight loss is a natural outcome of this degenerative disease. Naturally, eating involved not only food intake but also many other social and psychological process, which would need intact brain functions.

In the advanced stage, if weight loss progressively develops over a short period of time and the patient refuses to eat, the physician may prescribe tube feeding, since it is general opinion that food intake should not be waived.

5. Is tube feeding a solution against malnourishment for people with dementia?

Food intake problems which occur in the late stage of dementia may lead physicians and family members to decide on tube feeding. Nowadays dementia cases account for 30% of all tube feeding utilization [CALLAHAN et al 2000] [MITCHELL et al 2003].

5.1. Types of feeding tubes

To ensure food intake and nutritional needs are adequate, tube feeding formula is delivered through a 5-12F[106] tube, given directly into the stomach (enteral) or blood vessel (parenteral). Enteral nutrition has been practiced since ancient times in Greece and Egypt. Medical practitioners at that time used enemas[107] from wine, milk, whey, and wheat and barley broth to treat bowel infections [HARKNESS 2002]. In medieval times, sources reported initial usage of various tubes to transfer food to the esophagus or via the nasopharyngeal passageways. Modern tube feeding as we now know it, has existed since the 1980s.

At the moment, there are 5 types of feeding tubes, categorized by access route.

106French unit. 1 F = 0,33mm
107Nutrient enema is a way of providing nutrition through rectum.

Types	Inserted through	Feeds into
- Nasogastric tube (NG-tube)	Nose	Stomach
- Nasojejunal tube (NJ-tube)	Nose	jejunum
- Gastrostomy tube (G-tube)[108]	Abdominal wall	Stomach
- Gastrostomy- Jejunostomy tube (GJ-tube)[109]	Abdominal wall / Abdominal wall	Stomach and Jejunum
- Jejunostomy tube (J-tube)		Jejunum

Table 19: Types of feeding tube

The type of feeding tube usually used for dementia patients is a Gastrostomy-tube, in which an endoscopy procedure is needed. Annual cost for tube feeding is 450€, in Germany and Austria, and this is covered by medical insurance.

Application of a feeding tube allows physicians to control nutrient intake through choosing formula adjusted to the patients condition and specific needs. Many types of commercial formulas are available on the market, including e.g. polymeric formula, monomeric, fiber-containing, disease-specific formula, and special formula contained micronutrients. Moreover, it is also easier to determine mealtimes, since many dementia patients have disturbances in biorhythm time and sleep pattern.

5.2. Application of feeding tube for demented patients

Once a patient stops eating, due to dysphagia or other risk factors described in previous chapter, physician usually prescribe tube feeding to ensure nutritional intake. But advantages in using a feeding tube for demented patients is still much

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108Gastrostomy tube is also called PEG-tube (Percutaneous Endoscope Gastrostomy).
109Gastrostomy Jejunostomy tube is also called TJ-tube (Transgastric-jejunal).

debated. Benefits cited by those who support tube feeding include (i) prevention of malnutrition, (ii) prevention of complications of decubitus ulcer and (iii) aspiration pneumonia, (iv) to extent life, and (v) improve quality of life by providing comfort [MITCHELL et al 2000]. Each of these options will be discussed in the following passages. Other non-medical advantages according to the literature are a shorter hospitalisation time, less effort for nurses, as well as supporting culture and religious belief[110].

5.2.1. Preventing the consequence of malnutrition

Data regarding this matter are inconsistent. Some studies oppose the notion that tube feeding would help to prevent the adverse health effects of malnutrition. One clinical cohort study with 40 tube-fed patients showed that weight loss, reduction of lean body mass, and micronutrient deficiencies continued even if sufficient amounts of nutrient were provided [HENDERSON et al 1992] . Another study even found that, along with extended duration of tube feeding, cases of weight loss increased in amount and frequency [KAW and SEKAS 1994]. It was also noted that nutritional parameters, like hemoglobin, albumin, hematocrit and cholesterol did not improve after tube feeding application [HENDERSON et al 1992].

A constant body weight, even if subnormal below standard BMI , in advanced dementia is considered normal. This subnormal weight could be caused by low metabolic rate due to LBM shrinkage, athropic brain, or a physically inactive life. The body may also adapt to weight loss history by reducing its metabolic rate . [HOFFER 2006]

110In some cultures and religions, providing food for the old and the weak is considered an obligation. Some people may feel tube feeding as a way to fulfill this obligation.

5.2.2. Preventing decubitus ulcer

Decubitus is skin lesions, caused by continous pressure on the skin on one spot, mostly by lying in one position for too long and thus causing circulatory problem and damage to the skin and tissue underneath. Elderly people become prone to such bedsores because many risk factors are correlated with old age, such as immobility, incontinence, sensory loss, as well as poor nutritional status [ALLMAN 1997].

Weight loss and reduced muscle mass may increase pressure on bone areas. Certain nutrients such as amino acids arginine, vitamin A, B, C, minerals selenium manganese, zinc and copper, play a role in wound healing in animal experiments but this is not evident in humans. A diet rich in energy and protein may promote healing in human subjects [MALTHUS-VLIEGEN 2004].

Thus, theoretically, deployment of a feeding tube is intended to improve nutritional status through ensuring an intake of energy and nutrients for the elderly who could not maintain regular oral feeding. But data from the literature seems inconsistent to this hypothesis. One study that investigated the effect of tube feeding on nutritional status and development of decubitus on hip fracture patients failed to show improvement in incidence, development and severity of pressure ulcers [HARTGRINK et al 1998]. Although nutritional intake may be significantly higher with tube feeding, especially using high protein formula, there is no evidence that better nutritional status would improve clinical outcome in cases of decubitus [THOMAS 2001].

Additionally, complications from tube feeding may bring contradiction, diarrhea, fecal incontinence and restriction to mobility could make worse. In case of bedsores, oral feeding is prefered [MALTHUS-VLIEGEN 2004].

5.2.3. Preventing risk of aspiration

Aspiration occurs when food or gastric content are inhaled into the respiratory tract. Aspiration blocks airways and brings bacteria into the lung[111], and may result in death. In fact, pneumonia, in addition to infection of pressure ulcers, is one of the main causes of death in the elderly with dementia. In advanced stages of dementia, aspiration often occurs in cases of patients who have swallowing difficulties, thus tube feeding installation may aim to prevent aspiration and subsequent pneumonia.

Current data showed no decrease in the risk of aspiration pneumonia after application of tube feeding [LI 2002] [BOURDEL-MARCHASSON et al 1997]. In one study, risk of aspiration even increased in the tube feeding group (58%) compared to patients without feeding tube (17%) [PECK et al 1990]. This may be due to the fact that aspiration is also one of the complications in tube feeding.

5.2.4. Prolonging life

Physician and family members hope for prolongation of life as an effect of feeding tube placement, this is based on the assumption that food intake is unbearable for the functioning of body metabolism. However a few studies have found that patients with tube feeding did not have any advantage in the survival rate during the survey [MITCHELL et al 1998]. Studies suggest for dementia patients in advanced stages, the survival rate is not extended by the use of tube feeding [MEIER et al 2001]. With or without feeding tube, the mortality rate in end stage dementia is around 6 months [MEIER et al 2001], and in the tube fed group, life-span is only approximately 7,5 months after application [FINUCANE 1999].

111Pneumonitis is the aspiration of gastric content that may cause inflammation of lung tissue.

Experts suspect, when it is near the time of death, time, life cannot be prolonged again, even with tube feeding. Eating problems and dysphagia may indicate the terminal stage of dementia [GILLICK 2000].

Perhaps the physiological condition of patients in advance stage dementia is too debilitating to gain benefit from tube feeding, whereas complications from feeding tube attachment could add suffering [LI 2002].

Nevertheless, Rudberg et. al. in their study showed that residents of a nursing home with feeding tube were less likely to die compared with residents without tube feeding, even if the differences is not much [RUDBERG et al 2000]. In this trial, the survival rate for patients with feeding tube after 1 year is 50% , while residents without feeding tube is 39%.

5.2.5. Improving the quality of life

It is difficult to assess the quality of life in patients with dementia. Firstly, they may not able to communicate, and cognitive ability has been reduced as well. Since there is no data, knowledge about hunger sensation and thirst during the dying process could be interpolated from cancer patients. They report that they don't feel much hunger or thirst and this could be alleviated with minimal intervention, such as the application of swabs or ice chips [MC CANN et al 1994]. They may not feel they are starving, despite the fears of family members.

Placement of a feeding tube may discomfort the patient's daily life, since they often do not understand the purpose of the tube and usually try to pull it out [GILLICK 2000]. Restraint in the form of mittens is usually used which could add more stress to patient [PECK et al 1990] and increase the use of sedative [LI

2002]. Feeding tube placement may also reduce personal contact with caregivers [SYNOFZIK 2007].

Furthermore, as medical intervention, additional complications due to tube placement may appear. In fact, in older patients, up to one-third experience transient gastrointestinal complications, such as vomiting and diarrhea [CALLAHAN et al 2000]. Tube dislodgement , blockage and leakage are also common [FINUCANE 1999]. Even if major complications are rare (only 1-2%).

5.2.6. Conclusion concerning the benefit of tube feeding

Overall, data from the literature fail to show beneficial outcomes of tube feeding for elderly with dementia.. But benefit should be distinguished from effectiveness; tube feeding may be effective to ensure nutrient intake with some patients. Indeed, tube feeding can be used in certain situations in dementia care, such as a case of a patient with dysphagia and still having cognitive function, also for independent patients who are still able to move, but whether it will benefit and be appropriate in the terminal stage, is a controversial matter of debate [MARCKMANN 2007].

Dementia is a terminal illness, where possibilities of recuperation within current medical knowledge do not exist. Application of tube feeding should therefore consider realistic treatment goals, either prolongation of lifetime even in a vegetative condition or providing comfort and quality of life.

However, results from studies available to date do have some limitations:
  – Most of the available data concerning tube feeding in the late stage of
    dementia are based on observational studies, retrospective studies, or data
    extrapolated from mixed population [LI 2002]. Ethics, social and procedural

difficulties may complicate the designation of a good randomized controlled trial [MITCHELL 2007] and to date there is still no randomized clinical trial that has been performed [FINUCANE et al 2007].

- – Another problem is that existing studies so far do not distinguish the many forms of dementia nor different stages of dementia at which feeding tube are initiated among patients [SYNOFZIK 2007].

- – Difference in patients cohorts may also bias the result, since patients who receive feeding tubes may be weaker than those who do not. Studies may include patients with different health conditions in the same group [MC NAMARA and KENNEDY 2001].

- – Selection of an appropriate control group could lead to bias results, e.g. if the control group were hand-fed by loving family members compared to those fed by nursing assistants in nursing homes.

- – Some studies do not specify whether gastrostomies or nasogastric tubes are being assessed [REGNARD et al 2010].

Due to the lack of solid evidence, the question remain open, whether tube feeding really does harm, has no effect or is beneficial for the demented patient. Studies in the future should also assess outcomes such as patient distress, symptoms of malnutrition, hospital admissions, administration of medications. On the other hand, survival rate is perhaps not a relevant outcome measure for a terminal illness such as dementia [REGNARD et al 2010].

5.3. Patients and physician's preference of tube feeding

Decision making whether to use a feeding tube is affected by a number of factors such as age, gender, race, cultural factors, education, current health status at the time the study was conducted, and functional status [GARRETT et al 1993]. Some studies have surveyed opinions of elderly subjects regarding the feeding tube placement.

As data showed below, preference of tube feeding from medical workers is quite high. Some still regard tube feeding as a solution for patients with advance stage dementia. Aside from subjectively perceived benefit, one reason why tube feeding is preferable, is perhaps the fear of being accused of neglect [MC NAMARA and KENNEDY 2001]. Other reasons may be because tube feeding application is simple and convenient, but decision making should not be based on the convenience of the carers, but the patient's best interest must be prioritized.

Author	Subjects	Results
Gjerdingen et al 1999	84 non-demented elderly over 65y	Only 4 % agree to be tube fed. The proportion of those who do not prefer to tube feeding rise with the progressing severity of dementia
Carmel 1999	987 Israeli elderly	22% accept tube feeding
O'Brien et al 1995	379 American nursing home residents	One-third agree to tube feeding. Perhaps nursing home residents are used to see patients on tube feeding.
Reilly et al 1994	218 community-living Americans age 60-87	43% would want to be tube fed Subjects have a better education, thus perhaps the result is not relevant for general population
Emanuel et al 1991	405 patients from all ages in Boston's Massachusetts General Hospital	73% refuse tube feeding in case of dementia, while 82% refuse in case of dementia with terminal illness
Gerety et al 1993	52 nursing home residents	38% agree to tube feeding in severely physical disability state, 25% accept tube feeding in persistent vegetative state

Table 20: Preference of elderly to tube feeding methods [MC NAMARA and KENNEDY 2001].

Author	Subjects	Results
Carmel 1999	339 physicians	74,6% physicians prefer to tube feeding (versus 22% elderly)
Hasan et al 1995	199 geriatricians, speech therapists, dieticians, and nurses	47% agree of tube feeding utilization in case of dementia with food refusal
Norberg et al 1994	149 nurses	Nurses in Australia, Canada, Sweden often chose not to tube fed, they give high rank to ethical principle of autonomy Nurses from China and Israel prefer tube feeding, giving high rank of sanctity of life

Table 21: Opinions from physicians and nurses regarding tube feeding application

5.4. Maintaining oral feeding in elderly with dementia

Another option in feeding demented patients is oral[112] or hand feeding. The preference for oral feeding is often expressed in the assertion that it is said to preserve the quality of life for the demented patient. But what does quality of life means for the elderly with dementia, who have already partially lost their cognitive function?

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[112] Oral feeding is defined as intake of food through swallowing act.

5.4.1. Definition of the quality of life for elderly with terminal illness

Kohlmann [2000] measures the quality of life through physical constitution, physiological condition, social relationship and activities of daily living. In geriatrics, the term quality of life is often equated with well-being, which shows how subjectively perceived well-being being is emphasized in the care of elderly people.

Social demographical variables such as housing, financial conditions have less attention in determining the well-being of terminally ill demented patients. The following tend to be emphasised : (1) the patient's own state, including physical and cognitive functioning, psychological state, and physical condition; (2) quality of palliative care; (3) physical environment; (4) relationships; and (5) outlook [COHEN and LEIS 2002].

In BASE trials[113] on over 70 year old elderly demonstrate, there is more correlation between well-being and the subjectively perceived health condition, than the objectively measured health condition [SMITH et al 1999] . Moreover, the subjectively perceived health condition could predict mortality better than the objective measured health parameter.

Food is not only about nutrition, but also about comfort[114], taste enjoyment and social interaction. Food also symbolizes nurture and caring[115]. Since eating is one basic right of human life, oral feeding is regarded as one way of preserving human dignity in late life. Thus, eating and drinking is an important aspect in the quality of life and should be encouraged and maintained as long as possible [STEPP and

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113BASE stands for Berliner Altersstudie.
114Food intake can be comforting through its effect on hormones, triggered by some substances such as theobromine in chocolate.
115Food as a symbol of nurture and caring is originally come from mother and child relationship, feeding a baby is considered an expression of maternal love.

PAKIZ 2001].

In conclusion, the argument from supporters of oral feeding are, that hand feeding may increase the quality of life through providing more comfort for patients with dementia, it also preserves contact with caregivers and food enjoyment [SYNOFZIK 2007].

5.4.2. Oral feeding problems and risk of aspiration

To understand the oral feeding problems, four main areas need to be addresses:
- the pre-oral phase[116] of eating, intra-oral bolus preparation[117] and swallowing
- function of respiration
- the diagnosis, treatment and complications of the underlying medical condition
- environmental factor, including availability of carers

[Royal College of Physicians 2010].

The pre-oral phase, intra-oral bolus preparation and swallowing
In case of AD, pre-oral phase may be disturbed by changes in conduct and behaviour, agitation, loss of appetite, problems using cutlery, and restlessness. A good dental care and function of the nervous system are required to assure intra-oral bolus preparation.

Swallowing is a complex mechanism, it involves laryngeal elevation , laryngeal closure, opening of the upper oesophageal sphincter, bolus transit from mouth to

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116Pre-oral phase includes e.g. choosing the order in which the food is to be presented, salivation and other behavioral response, as well as social interactions.
117Intra-bolus preparation depends on dentition, salivation, chewing, and control of the bolus by the muscle of the tongue.

oesophagus and subsequent return of the involved structures to their starting positions In a swallow, respiration is normally arrested, otherwise bolus will be inhaled. Coughing is a protective response to avoid aspiration. Indeed, the risk of aspiration is the main concern of oral feeding [Royal College of Physicians 2010].

The advanced stage is usually marked by swallowing difficulty, although dysphagia may also occur in early stages of dementia [PRIEFER and ROBBINS 1997]. The reasons why dysphagia is often regarded as a terminal symptom are poor screening, atypical presentations and carer adjustment to its presence [REGNARD et al 2010].

To assess oral feeding problems, records of food history and examination such as observation of eating and drinking in periodical intervals are necessary before planning strategies to improve food intake.

5.4.3. Feeding plan – examples from nursing homes projects

Practice of oral feeding have been performed in some nursing homes, such as:
– "Finger food" and   "Eat by walking"
– "Cooking at bedside"
– "Lunch club"

In his book, *Essen als basale Stimulation*, Markus Biedermann offer some eating concepts for nursing home residents with dementia in Switzerland. Through stimulating senses other than taste, such as sight, touch, smell and hearing, he tries to make mealtime an experience as pleasant as possible for residents.

Finger food characterizes food taken by hand, without any cutlery or tools and usually cut into nibbles. They are favored for residents with motoric or cognitive

disturbance, and thus could spare the use of eating utensils. Hindrance probably emerges from background experience, for some elderly eating with the hand is still considered barbaric and uncivilized, as they were taught by their parents not to eat with fingers since childhood [BIEDERMANN 2004]. Hygiene and the way to eat with fingers should be considered. A trial in an Alzheimer's care facility in Ohio during two six months periods found, that a change in menu with more finger food did not result in weight gain, but typical weight loss did not occur and food consumption patterns significantly increased. Inclusion of finger food in the menu is an appropriate feeding method for AD residents [SOLTESZ and DAYTON 1995].

The eat by walking concept is a further development from finger food*.* This program aims for dementia patients who are constantly moving, wandering around and can't sit quietly at a table. Finger food is put in strategic places, where they often pass by.

Mary Marshall from the Dementia Services Development Centre Stirling University Scotland, believed that eating disorders are not necessarily a consequence of dementia, but rather a reaction to stress. Therefore, she developed a project called *Lunch Club*, a program where a small group of the elderly with dementia have a lunch with healthy persons once or twice a week. During mealtime, stress reduction is achieved through a comfortable dining atmosphere in a pleasant place, limitation of distraction, a little small talk, and so on. This program gives a chance to elderly with dementia to take part in community activities, because living in care homes does not mean that the elderly should give up outdoor activities [Dementia Service Development Centre 2002]. These oral feeding practices, namely finger food /eat by walking and lunch club, could only be applied if residents are still mobile.

The cooking at the bedside project was conducted in care homes Sonnweid and Kühlewil in Switzerland. Six previously chosen bed-ridden demented patients participated in this experiment and their reactions were observed. Preparation was done in the kitchen, with simple recipes and simple utensils, food is cooked in the patient's room for only about 5 minutes, and during this "animation" time food was served. Reactions such as drooling, changing in expression, and eating more than usual was observed during the experiment, although these reactions only last for about 5 minutes. Although the project was successful, it should not become routine program in nursing homes, since the stimulating effect probably lessens if applied too often [BIEDERMANN 2004].

5.4.4. Strategies to support oral feeding

Improved feeding techniques may minimize the risk of aspiration, facilitate eating and drinking, and eventually reduce the prevalence of malnutrition in demented patients. Depending on mobility and cognitive functions, some of these actions are applicable to patients in mild to moderate dementia, namely with feeding problems. At the end of life, these measures are hardly useful. Some suggestions are listed in table 23.

Factors	Strategies
Modifications of food and fluids	– Shape, texture and food consistency are adjusted to the ability of chewing, swallowing, and health conditions. – Elderly people usually prefer a small portion, strong spices, familiar recipes, sweet taste. – Providing a high quality and nutritious food, with supplementation if necessary. – Avoid solid particles in food. – Arranging a nice food presentation. – Consider wishes and favorite food of patients.
Oral feeding strategies	– Organizing frequent small meals – Use specific utensils – Considering personal ritual
Swallowing strategies	– Reduced sensation may be helped by a thermal stimulation with ice or chilled material applied to the oropharyngeal musculature
Positioning and postural techniques[118]	– These include chin tuck, head rotation to the affected side, head tilt, side lying or remaining upright
Environment and external strategies	– Create a comfortable dining atmosphere, without unnecessary disturbance/ stimulus, e.g. with simple room decoration, relaxing music, or provide a pleasant smell of food – Giving patients enough time to eat. – Present an aquarium[119] in dining area. – Making mealtime a pleasant social event

118Postural techniques are useful to change direction of the bolus.

119According to one study, the presence of aquarium in dining room can increase nutritional intake of demented patients. The effect is based on the assumption, that contact with natural surroundings may reduce stress [EDWARDS and BECK 2002].

Other options	– Minimize adverse medication effect by prescribing fewer medications which could affect appetite. – Individual supervision during meals. – Encourage physical activity if still possible. – Relieve stress.

Table 22: Strategies to improve meal services in feeding elderly with dementia [Royal College of Physicians 2010] [HIRSCH 2004].

To ensure a successful implementation of the oral feeding intervention, good and effective cooperation and communication among the patient, the family, nurses, kitchen staff, physicians, SLTs, nutritionists and other medical workers involved are necessary. Multidisciplinary approaches on the feeding problem may offer the optimal solution and hazard may emerge from a one-sided view. One study from the US showed nursing homes that employed SLTs had a higher rate of tube feeding application on its residents. Nutritionists could also focus only on nutrient intake and recommend tube feeding [MITCHELL et al 2003].

An important factor that was often not included in studies is the role of caregivers. Carers may suffer mental or physical health problems due to constant caregiving activities. Since most patients are dependent on their carers, their interaction may impact the quality of life of the person with dementia. In one study, feeding difficulties were significantly associated with the age and behavior of the caregiver [RIVIÈRE et al 2002]. To improve caregivers' well-being, dementia management should also include programs such as training to improve knowledge in medical treatment, psychological service to reduce stress as well as training to improve communication skills.

5.4.5. Evidence of effectiveness of feeding interventions in literature

A systematic review of feeding interventions in patients with dementia are showed in Table 23. Although not all studies showed positive results, some surveys indicated, that high caloric supplementation could be beneficial to gain weight, but physical and cognitive function did not improve during trial [LAURA et al 2011].

Study	Subjects	Intervention type	Outcomes	Difference
Beck, 2002	66	Liquid supplement	Weight	No
Carver, 1995	46	Liquid supplement	Weight	Yes
Cereda, 2009	28	Liquid supplement	Pressure ulcer healing	Yes
Gazotti, 2003	80	Liquid supplement and soup	Weight	Yes
Gil Gregorio, 2003	99	Liquid supplement	BMI, morbidity and mortality	Yes Yes No
Kwok, 2001	47	Milk powder	Weight Cognition Physical function	No No No
Lauque, 2000	78	Liquid supplement Soup, fruit and dessert	Weight BMI Grip strength	Yes No No
Lauque, 2004	91	Liquid supplement Soup, dessert	Weight BMI Cognition Physical function	Yes Yes No No
Parrott, 2006	30	Liquid supplement High calorie bar	BMI	Yes
Planas, 2004	44	Liquid supplement	BMI Cognition	No No
Wouters-Wessling, 2002	35	Micronutrient-enriched liquid supplement	Weight	Yes
Wouters-Wessling, 2006	34	Liquid supplement	Weight Physical function	Yes No
Young, 2004	34	Liquid supplement High-calorie bar	Weight	Yes

Table 23: Studies on the effect of high caloric supplementations for patients with dementia [LAURA et al 2011].

Study	Subjects	Intervention type	Outcomes	Difference
Beck, 2008	121	Chocolate Hot chocolate Homemade supplement Exercise	Weight BMI	Yes Yes
Crogan, 2006	61	Individualized nutrition therapy process and care plans	BMI Physical function	No No
Goddaer, 1994	29	Relaxing music played at lunchtime	Behaviors	Yes
Keller, 2003	82	Enhanced dietitian time and menu	Weight	Yes
Remsburg, 2001	40	Buffet-style dining program	Weight	No
Robbins, 2008	515	Chin-down posture Thickened liquids	Pneumonia Mortality	No No
Salas-Salvado, 2005	56	Lyophilized foods	Weight	Yes
Simmons, 2005	17	Megestrol acetate and feeding assistance	Weight	No
Simmons, 2008	69	Feeding assistance	Weight BMI	Yes Yes
Volicer, 1997	12	Dronabinol	Weight Negative affect Disruptive behavior	Yes Yes No
Yeh, 2000	68	Megestrol acetate	Weight	Yes
Young, 2005	34	Meals high in carbohydrates	Weight Cognition Behavior	No No No

Table 24: Summary of evidence for feeding interventions [LAURA et al 2011].

Towards the end of life, eating difficulties may become worse, also severe health conditions may leave little room to intervene with an oral feeding program. As food and fluid intake lessen, a decision has to be made whether to apply tube feeding or to continue the assisted oral feeding with all the attendant risk and benefit. In practice, the decision to apply or withdraw tube feeding is not always easy, since it is also influenced by other factors, such as ethics and the law.

6. Feeding options in the terminal stage of dementia

In the terminal stages, demented patients usually lose interest in eating and drinking and eating difficulties become more severe, resulting in poor food intake and subsequent symptoms of malnutrition. Artificial nutrition and hydration (ANH) is often used in such cases, in the form of either NSG or PEG.

In general, there are 4 feeding options for the elderly [Royal College of Physician 2010] :
  – full oral feeding
  – a combination of oral and non-oral feeding
  – palliative feeding using small amounts of food, mainly for enjoyment
  – alternative nutrition using non-oral methods

Making a decision as to which feeding option is applicable in case of terminally ill patients with dementia, is difficult and loaded with emotional, ethical and perhaps in some cases also legal issues. The patient's deterioration in cognitive function and inability to communicate in the end stage make it impossible to ask directly his/her wish.
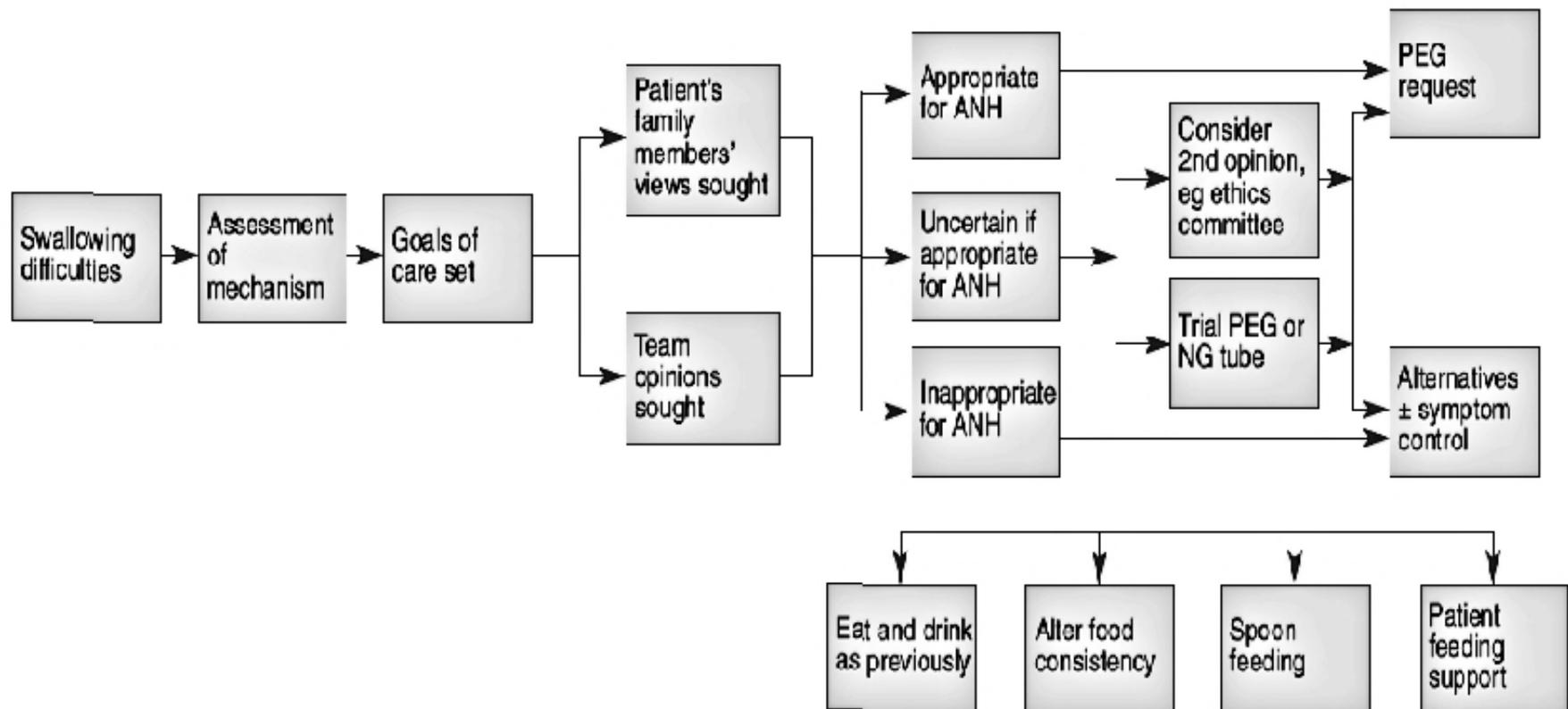
Illustration 11: Decision making in patients with feeding problems [Royal College of Physicians 2010]

6.1. Benefit of oral versus tube feeding from medical viewpoints

To date there is no direct comparison between tube and oral feeding for demented patients in the end of life, and such trials may be difficult to design [GARROW et al 2007]. The literature shows that oral feeding does not offer health benefit regarding risk of aspiration and mortality [HANSON et al 2011] except to avoid medical intervention at the time of application, as well as complications and restraint caused by the feeding tube application. On the other hand, application of tube feeding do not provide medical benefits as described in previous chapter.

In this case, physicians together with family members should determine a realistic treatment's goal, so as to preserve the quality of life until the last moments. From the medical point of view, this can be reached partly by avoiding burdensome and unnecessary medical interventions.

Some evidence proposes that the human body can not utilize or digest nutrients and fluid anymore in the end of life phase. Dehydration and starvation for dying patients may stimulate the release of natural anesthetic, that promote comfort during the last hours of life [ELLERSHAW et al 1995]. Giving artificial nutrition and hydration may lead to excess and overload, adding physical metabolic burdens in the form of edema and aspiration, also prolonging suffering.

Distinguishing wasting illness with insufficient nutrient intake would be important [FINUCANE et al 2007]. They may show the same symptoms, but require different treatments. While malnourished patients can get benefit from nutritional intake including from feeding tube, a wasting syndrome requires more complex treatments and usually appear in the last stages of incurable disease.

6.2. Ethical and legal issues regarding the use of tube feeding for demented patients

The application of tube feeding in terminally ill demented patients raises ethical questions, concerning the principle of beneficence, non-maleficence, respect for autonomy and the principle of justice[120] . Beneficence in medical ethics proscribes that any medical treatment should bring benefit for patients. Tube feeding for an ethicist is considered medical intervention [GOLDSTEIN and FULLER 1994], although there was debate whether it falls under definition of a treatment or basic care[121]. As a medical treatment, the risk and benefit should be carefully looked at and weighed up before deciding its application (principle of double effect[122]).

Principle of beneficence and non-maleficence

As described in the previous chapter, from data currently available, the benefit of tube feeding for patients with advanced stage dementia is not convincing and mostly subjectively perceived. Expectation in improved nutritional status, prevention from pressure ulcers and aspiration or life prolongation was not proven. Moreover, it seemed that complications from tube feeding may even exacerbate the patient's condition. And it contradicts with *primum non nocere[123]*, also known as the principle of non-maleficence*.* [SYNOFZIK 2007].

Human autonomy and dignity

A consequence of progressive cognitive deterioration is loss of autonomy. Autonomy is defined as the right to determine one's own destiny, the right to know, to choose and not to be harmed [MC FIE 1996].

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120 According to Beauchamps, principles of beneficence, non-maleficence, autonomy and justice are principles of ethics applicable in health care [Beauchamps, Childress 1977].

121The basic care here implicates eating and drinking.

122Often in health care, "do good and avoid evil" could not be applied in the same time, since every medical intervention always has risk of complications (*principle of double effect*). A treatment is considered "safe" if the benefit/effectiveness surpass the risk/maleficence   [Goldstein, Fuller 1994].

123Primum non nocere means first do no harm.

In the case of patients with advanced stage dementia, where they may be unable to express their opinion, autonomy is shown in the form of advance directive [MC NAMARA and KENNEDY 2001]. It contains the preference of medical treatments or appointment of a trusted individual[124], who will make decisions in case the patient is incapable of making informed decisions for themselves, although in most situations decision-making is dominated by the physician and medical team [VAN ROSENDAAL et al 1999]. In the case that the patient is unable to make informed decisions, a health care proxy should decide, based on knowledge about the patient's wishes and best interests.

Legal power of advance directive differs in each country. In 2006 Austria has endorsed a regulation about advance care directive, where patients have the right to refuse medical treatments but not nursing care. Tube feeding is considered by some scholars as a medical treatment , but if artificial nutrition and hydration is seen as basic nursing care, withdrawal from tube feeding would mean euthanasia[125] and is still illegal. Since medical knowledge develops rapidly, Austrian regulation requires advance directives to be renewed every 5 years [WALLNER 2007] .

If an advance directive and health care proxy are not available, the decision is made by family members, physicians and court, respectively[126], though automatism should be avoided [PEINTINGER 2004], out of respect for the patient's autonomy. At first, surrogate decision makers should be clear about any treatment's objective. Tube feeding may be applied in the early or middle stage, while patients are not dying and as a reconciliation step after a medical intervention, and it should be checked regularly whether it is still consistent with

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124In the legal term, this person is called durable power of attorney or health care proxy.
125Euthanasia defines the termination of one's life in order to relieve suffering.
126[Austrian *Patientensverfügungs-Gesetz* 2006]

the treatment's objective [WALLNER 2007].

Without an advance directive, some ethicists may consider PEG as a form of force feeding, since nutrient intake without consent of patients and may be counted as bodily harm. Use of restraints to keep the feeding tube in place could also mean violation of dignity [SYNOFZIK 2007].

Debate emerges as to whether withdrawal of tube feeding; a life-sustaining piece of equipment in case of severe demented patients, falls under the definition of euthanasia[127]. Euthanasia is illegal in most countries, except for the Netherlands, Switzerland, Thailand, part of Spain and the US.

Based on a treatment's objective to assure the quality of life, withdrawing and withholding a burdensome medical treatment such as tube feeding should be seen as allowing the dying person to die in appropriate way. It should be seen in a different perspective, unlike patients with persistent vegetative state (PVS).

6.3. Financial matters

6.3.1. Cost, effort and incentives

For nursing homes, an oral feeding program is resources consuming, more time, finance and work are needed to provide good quality of food and hand-feed service. Each patient requires 35-40 min per meal [SIMMONS and SCHNELLE 2006] , and it also means an expensive labor cost**.**

127Passive euthanasia defines as omission of life-sustaining treatment, which lead to death.

To provide a hand feeding service for its demented residents, nursing homes need to organize a system where interdisciplinary team members can share information and develop effective and efficient methods together.

One retrospective study compares cost of the hand feeding versus tube feeding in one nursing home in Boston over a 6 months period. The results showed that hand feeding cost more due to the demands placed on time and labor resources [MITCHELL et al 2003]. However, reimbursement from Medicaid (an insurance company in the US) is higher in the case of tube feeding. This consideration is based on the initial feeding tube placement and hospitalizations visits for the management of complications of tube-feeding. The reimbursement rate for tube feeding in the US state of Maryland is also higher than hand feeding, although the cost for hand feeding is higher. These financial advantages may promote the high utilization of tube feeding [FINUCANE 2007].

6.3.2. Incentives for health care facilities

Although it should not be considered as the main point in decision making, tube feeding is easy, faster and needs less effort. Whereas implementation of hand feeding needs creativity, to assess possible risk factors, and then try to find solutions appropriate for each situation.

For nursing home facilities and physicians, tube feeding gives a proven solid documentation regarding implementation of basic care[128]. Since it is a widespread assumption that malnourishment could be a result of neglect in care treatment, tube feeding protects nursing homes from the accusation that its resident died

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128Some literature data still consider tube feeding as a basic care, namely by providing (artificial) nutrition and hydration; while others may think of it as medical intervention. There is still no legal regulation or consensus to this issue.

because of neglect in providing sufficient nutrition and hydration [SHEIMAN and POMERANZ 1998].

Regulation may support facilities to place tube feeding on its residents. Federal guidelines of Maryland stated that each nursing home facility must assure each resident maintains acceptable parameters of nutritional status, such as body weight [FINUCANE 2007]. Again, tube feeding proved that adequate provision has been done and would protect facilities against tort litigation. Different federal laws in each state of the US may cause variable rates of feeding tube application [PASMAN et al 2005].

6.4. Emotional and psychological concerns

For caregivers and family members the decision to apply a feeding tube may be loaded with emotional issues. Fearing that a patient may die if the tube feeding option is refused, feeling guilty because a patient refuses to eat, or cannot bear to "let him starve" are common arguments. Additionally, caregivers may be afraid of burdensome care by providing oral feeding [CALLAHAN et al 1999]. Moreover, the emotional symbol of food and water represent nurturing and care-giving, and withdrawal of food is considered as punishment or protest action [CRANFORD and ASHLEY 1986]. Thus to justify perception, caregivers may feel obliged to provide nutrition as a form of nurture.

A mental trait of modern society is a feeling of having to "do something" in case something goes wrong or badly. It may be difficult for a medical team to be seen "not doing anything". They may feel powerless or afraid of the consequence of law and accusations of malpractice. This phenomenon results in the medicalisation of

dying[129], where people loses the capacity to accept death and suffering as an aspect of life [CLARK 2002].

New ways of thinking and change of mindset are required to fix such presumptions and wrong basic assumptions about the meaning of nutrition and hydration in the last stage of dementia.

6.5. Social , religious and cultural issues

Decision making processes usually depend on the patient's or family member's personal views about life and death. Culture and religion have a great role here and physicians need to be sensitive to these matters. Reasons such as hoping for a miracle, refusal to give up on the God of faith, a conviction that every moment of life is a gift from God and is worth preserving at any cost, and a belief that suffering can have redemptive value, can be used to justify aggressive medical intervention in end-of-life care [BRETT and JERSILD 2003].

6.6. Decision-making

The Royal College of Physicians provide a guide for family members with some considerations of decision-making. Support of professionals from other parties of expertise, such as from clinical ethics committees, court or religious leaders may also be helpful.

129Modern medical system regards death as something to be resisted, postponed or avoided. Palliative care is a response to calls for greater dignity at the end of life [CLARK 2002].

Consideration factors	Explanation
Advance directive	Presence of advance directive, to know patients wishes and priorities.
Ethical principles	Interventions with no beneficial effect should be ruled out.
Legal or financial concerns	There is a pressure on hospital to place PEG, so that the patients can be accepted in a nursing home.
Emotional factors	Provide knowledge to avoid guilt factors, good communication skill is required.
Cultural and religious background	Be sensitive and understanding about these issues.

Table 25: Considerations in decision-making

6.7. End-of-life care and dementia

In case tube feeding is withdrawn or withheld, an alternative is to hand-feed patients with food/thick liquid, that is prepared in such a manner as to avoid the risk of aspiration. Hand feeding may not be effective in preventing malnutrition, but it can maintain comfort in the patient's care [LI 2002].

Near death, it is more important to provide patients with comfort measures, such as pain and symptoms management, moistening the lips and good mouth care, frequent change of body position to avoid pressure ulcers and family support.

Palliative care is perhaps the appropriate form of care for persons in the terminal stage of dementia. In palliative care, efforts are intended to alleviate symptoms; pain relief, accompaniment and quality of life are prioritized over medical interventions. But there are some barriers to good palliative care for people with

dementia. It appears, dementia is still not being recognized as a terminal disease. This may be due to the unpredictable nature of the disease. There is no accurate prognostic marker for advanced stage dementia, which makes it difficult to recognize a terminal phase and predict life expectancy [SACHS et al 2004].

7. Discussion

Is there really a need for tube feeding placement for patients with dementia? How important is the optimal nutritional status for disease progression and in the terminal stage of dementia?

Many people, including physicians and medical workers, still consider a good nutritional status is important in disease progression. Indeed, malnutrition is associated with bad outcomes in the hospitalized elderly, but treating malnutrition does not always result in better outcomes. The relationship between malnutrition and illness severity is complex and not yet fully understood. Evidence from aggressive nutritional intervention such as tube feeding shows that benefit is limited to specific subgroups, such as patients with hip fractures or after abdominal surgery [COVINSKY 2002].

In the case of patients with dementia in the advanced stage, physicians may misunderstand the cachexia syndrome at the end of life as signs of malnutrition and thus will try with all means to keep nutritional status and intake at an acceptable level. A diagnostic tool to distinguish wasting syndrome with insufficient nutritional intake is urgently needed.

Tube feeding has no proven benefit for patients in advanced stages of dementia. Data from the literature shows a lack of efficacy in preventing malnutrition, pressure ulcers and pneumonia. Moreover, as a medical intervention, tube feeding has a risk of complication and may be burdensome. But the evidence is weak, study designs were poor and mostly observational. To date, there is no randomized clinical trial comparing tube feeding with hand feeding, and perhaps considering the linked ethical issues, such study will be difficult to perform. Further researches in this matter should consider a better study design, differentiation in

types of dementia, specified subject groups, reliable measurement tools and reasonable outcomes.

Since most data is based on the frail elderly in advanced stage of illness, there is an opinion, that PEG should be used sooner to maintain nutritional status and avoid malnutrition. But there is no available data to support such a view.

Criticism of tube feeding is based on a failure to show beneficial outcome, but hand feeding is not effective to improve the medical condition. The argument for a hand feeding option is that it treats patients more humanly, thus preserving the quality of life by giving them more possibilities for social interaction.

A new order, "comfort feeding only" (CFO) is probably be the ideal alternative. The feeding is comfort-oriented, the patient will be fed as long as mealtime does not cause distress to the patient. An individualized care plan, which focuses on treatment goals, is used to document signs of distress, favorite food, effective feeding techniques, and at what times of the day feeding is preferable. If the patient does not tolerate oral feeding anymore, the carer may continue interaction in the form of mouth care, speaking to the patient and giving therapeutic touch [PALECEK et al 2010]

Epidemiological data shows a high prevalence of tube feeding application in the case of dementia, indicating that some external factors may affect the decision-making process. The notion of food as a symbol of care and nurture makes it difficult for family members to withhold artificial nutrition, interpreting that this would mean letting the patient suffer from hunger. Thus, they may feel guilty and responsible for the patient's death. Solving this psychological issue will need a better understanding of disease progression, a reasonable treatment's goal, and public education to shape attitudes towards death. Proper use of language, such

as "comfort feeding" instead of "hand feeding" may help to clear misinterpretation and stress the patient's goal for care [PALECEK et al 2010].

Treatment for complications of dementia in terminal stages such as infections and aspiration, are usually a routine in hospital and relatively inexpensive, compared to the complications of cancer or congestive heart failure. For family members to choose palliative care simply means to forgo treatment that is not invasive and usually effective in the short run. This may be psychologically and emotionally challenging.

Financial incentives in the health care system appear to support utilization of tube feeding for dementia cases. A higher reimbursement for nursing facilities in the case of tube feeding instead of hand feeding is one example. With the current state of knowledge about the ineffectiveness of tube feeding, financial incentives need to be adjusted.

8. Summary

The rising prevalence of dementia cases demands a better understanding about the pathology and progression of the disease. Researches in recent years concentrated on prevention and development of medications. Nutritional imbalance may play a role in the pathology of dementia, through oxidative stress and inflammation, giving a hope that a modulation of nutritional factors may prevent or delay the onset of dementia. Antioxidant compounds, B-vitamins, ω-3 fatty acids, low caloric and low glycemic index carbohydrates diets, have been investigated concerning their involvement in the pathology of dementia with contradicting results. However, if implemented early in life, a healthy diet may present a potential preventive approach against dementia.

Observational studies show that feeding problems in dementia are common. Over time, the ability to eat orally decline in the elderly with dementia, and family members start to consider the utilization of artificial nutrition and hydration. From a medical point of view, tube feeding is ineffective prolonging life, avoiding malnutrition, healing pressure ulcers and avoiding the risk of aspiration. Benefits are likely to be perceived, clinging to the notion that adequate nutrient intake would improve the health condition. Severe weight loss perhaps indicates the terminal stage of the disease, thus weight loss could not be prevented even with invasive nutritional intervention such as tube feeding.

Decision-making is often difficult and loaded with emotional, ethical and legal issues. Considering the terminal nature of the disease, a reasonable care treatment will be to preserve the quality of life through comfort feeding and continued interactions. To support this, incentives in the health care system need to be adjusted.

9. Zusammenfassung

Die wachsende Zahl der an Demenz erkrankten Personen erfordert ein besseres Verständnis über die Ätiologie, Pathogenese und Verlauf der Krankheit. Die Forschung in den letzten Jahren konzentrierte sich in der Entwicklung von Antidementiva und in der primären Prävention von Demenzerkrankungen. Oxidativer Stress und Entzündungsprozess spielen eine wichtige Rolle in der Pathogenese von Demenzerkrankung, welche durch Ernährung beeinflusst werden kann. Die Bedeutung von antioxidative Verbindungen, B-Vitamine, ω-3 Fettsäuren und Kalorienrestriktion in der Pathologie von Demenzerkrankungen wurden in vielen Studien untersucht, zum Teil mit widersprüchlichen Ergebnissen.

Beobachtungsstudien zeigen hohe Prävalenz der Ernährungsprobleme bei dementiell erkrankten Menschen. Schluckstörungen verursachen, dass Menschen mit Demenz immer weniger zu sich nehmen und künstliche Ernährung wird eingesetzt um Mangelernährung vorzubeugen. Studien zeigen, dass PEG kein Nutzen haben um das Leben zu verlängern, Fehlernährung zu verhindern, Druckulcera zu heilen und die Risiken der Aspiration zu vermeiden. Die Vorteile sind meist nur suggeriert durch die psychologische Bedeutung der Ernährung. Im Fall von Demenz, Gewichtsverlust kann auf ein Endstadium der Krankheit hinweisen.

Die Entscheidungsfindung zur künstlichen oder oralen Ernährung kann die Angehörige mit emotionalen, ethischen und rechtlichen Fragen belasten. Demenz ist eine unheilbare Erkrankung, ein vernünftiges Ziel in der Pflege wäre die Verbesserung der Lebensqualität durch *comfort feeding* und kontinuierliche Bindung. Eine neue Anpassung der Leistungsanreize im Gesundheitswesen zu diesen Kenntnissen ist notwendig.

10.   Literature

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Wien, im Februar 2012