

REVIEW ARTICLE

Sleep Disturbances and Cognitive Impairment in the Course of Type 2 Diabetes-A Possible Link

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Abstract: There is an increasing number of patients worldwide with sleep disturbances and diabetes. Various sleep disorders, including long or short sleep duration and poor sleep quality of numerous causes, may increase the risk of diabetes. Some symptoms of diabetes, such as painful peripheral neuropathy and nocturia, or associated other sleep disorders, such as sleep breathing disorders or sleep movement disorders, may influence sleep quality and quantity. Both sleep disorders and diabetes may lead to cognitive impairment. The risk of development of cognitive impairment in diabetic patients may be related to vascular and non-vascular and other factors, such as hypoglycemia, hyperglycemia, central insulin resistance, amyloid and tau deposits and other causes. Numerous sleep disorders, *e.g.*, sleep apnea, restless legs syndrome, insomnia, and poor sleep quality are most likely also associated with cognitive impairment. Adequate functioning of the system of clearance of the brain from toxic substances, such as amyloid β , *i.e.* glymphatic system, is related to undisturbed sleep and prevents cognitive impairment. In the case of coexistence, sleep disturbances and diabetes either independently lead to and/or mutually aggravate cognitive impairment.

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1. INTRODUCTION

There is an increasing number of patients worldwide with sleep disturbances [1, 2] and metabolic disturbances, including diabetes [3]. Both sleep disturbances [4] and diabetes [5] may be associated with cognitive impairment or even dementia. It has not been fully elucidated whether sleep disturbances in the patients with diabetes are merely accidentally coexisting disorders or there is a bidirectional influence of sleep disturbances and diabetes, and whether cognitive impairment in the patients with diabetes - at least in a part of them - is in some way related to sleep disorders. Meta-analyses

contents of sleep disorders, diabetes, and cognitive impairment are presented in Table 1.

2. SLEEP DURATION AND DIABETES

Both long and short sleep duration may be related to diabetes incidence. Long sleep duration was positively associated with insulin resistance, as recently shown in the study of 2848 individuals [6]. In the other study, encompassing 355 type 2 diabetes (t2D) patients and 43 patients with impaired glucose tolerance, poor glycemic control, defined as glycated hemoglobin (HbA1c) level $\geq 7.0\%$, was markedly associated with short sleep duration [7]. In the population-based cohort study of 162 121 non-obese adults, short sleep duration (<6 hours/day) significantly ($p < 0.001$) increased the risk of elevated levels of fasting glucose by 6% [8]. In the Chinese study of 19 257 participants, both short and long sleep dura-

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Table 1. Meta analyses contents of sleep disorders, diabetes and cognitive impairment.

S. No.	Combination of Disorders	Refs.
1	Sleep duration and diabetes	[6-13]
2	Sleep quality and diabetes	[14-20]
3	Insomnia and diabetes	[10, 21, 22]
4	Sleep breathing disorders and diabetes	[24-29]
5	Diabetes as a risk factor for sleep disturbances	[41-49; 54-60]
6	Cognitive impairment during diabetes	[61-84]
7	Hypoglycemia and dementia	[66, 85-88]
8	Hyperglycemia and dementia	[89-95]
9	Brain diabetes and cognitive impairment	[96-137]
10	Functional impairment between sleep, diabetes and glymphatic system	[159-168]

tion was associated with an increased incidence of t2D [9]. But in the other analysis of 53 260 adults in China increased risk of diabetes was associated only with short (≤ 6 hours), but not with long sleep duration [10]. One night reduction in the sleep duration decreases insulin sensitivity [11], and subchronic sleep deprivation, lasting up to 8 days, causes peripheral insulin resistance [12]. Also, pre-diabetes occurs more frequently in people who sleep less than 5 hours per day [13].

3. SLEEP QUALITY AND DIABETES

Sleep quality strongly influences the risk of diabetes. The study of 2291 adults in the mean age of 46.3 ± 5.1 years revealed an increased risk of diabetes among subjects with chronically non-restorative sleep [14]. Poor sleep quality, as measured by a self-administered questionnaire, was associated with poor glycemic control in t2D patients [7]. There is a strong relationship between sleep quality and glycemic control in adult t2D patients [15]. A comparison of the group of 622 adult t2D patients and 622 age and sex-matched controls revealed poorer sleep quality in diabetic patients, as measured by the Pittsburgh Sleep Quality Index (PSQI) [16-18]. The study performed in 347 obese and overweight women with metabolic syndrome revealed significant correlation of insulin resistance with poor sleep quality, as assessed by Medical Outcomes Study Sleep Scale; especially sleep latency over 30 min, restless sleep and daytime sleepiness were all related to the homeostatic model assessment of insulin resistance (HOMA2-IR) values [19]. Multiple awakenings during the night reduce the sensitivity of cells to insulin [20].

4. INSOMNIA AND DIABETES

Primary insomnia seems to be one of the possible risk factors for developing diabetes. Patients with insomnia, especially younger than 40 years or with chronic insomnia lasting >8 years, were found to be at higher risk of developing t2D than the patients without insomnia [21]. Increased risk of diabetes was associated with difficulties in falling asleep and with early morning awakening [10]. However, in

the study of the patients with primary insomnia and normal polysomnography (PSG) recording, neither diabetes nor glucose intolerance were found [22].

5. SLEEP BREATHING DISORDERS AND DIABETES

Sleep breathing disorders, including obstructive sleep apnea (OSA) syndrome, frequently occur in diabetic patients [23-29]. The frequency of occurrence of sleep-disordered breathing among t2D patients is presented in the Table 2.

In the group of 5874 participants of the Sleep Heart Health Study, including 692 people with diabetes, PSG has shown a higher prevalence of periodic breathing in diabetic than in non-diabetic patients [30]. The comparison of the groups of the OSA patients with ($n=132$) or without ($n=264$) t2D, matched by age, sex, and level of obesity, assessed as BMI and neck and waist circumference, revealed higher apnea/hypopnea index (AHI) and more severe hypoxemia in diabetic than in non-diabetic patients [31].

There is also a significant association between insulin resistance and OSA [32]. Insulin resistance may be associated with OSA pathogenesis as obese, insulin-resistant subjects without diabetes or sleep apnoea demonstrated preclinical signs of increased pharyngeal collapsibility, indicating susceptibility to sleep apnoea [33]. These findings suggested that insulin resistance could play a significant role in sleep apnoea pathogenesis. On the other side, however, insulin resistance increases as a consequence of sleep fragmentation [20], and intermittent hypoxia [34], which are the typical consequences of OSA. Interestingly, there is a link between insulin resistance, OSA, and excessive daytime sleepiness (EDS) which is a typical sign of OSA syndrome occurring in most of the OSA patients. Insulin resistance was related to EDS occurring in OSA patients, independently from obesity [35]. The relation between EDS and insulin resistance has been confirmed in subsequent studies [36]. Patients with EDS and severe OSA had higher HOMA index – indicating insulin resistance – than the patients without EDS, independently from OSA severity [37]. However, presented associations are far from indicating a direct cause-effect relationship.

Table 2. The frequency of occurrence of sleep-disordered breathing among t2D patients.

Number of the Patients	Diagnosis	Frequency of OSA	Diagnostic Method	Author/Refs.
279	AHI >10/h	48%	one-channel monitoring device	[24]
	AHI >20/h	29%		
306 obese	AHI >5/h	86%	unattended PSG	[25]
	AHI 5-15/h	32.5%		
	AHI 15-30/h	30.5%		
	AHI >30/h	22.6%		
131	AHI >5/h	75.6%	in-home device	[26]
	AHI >15/h	40.5%	WatchPAT 200	
679	sleep disordered breathing	34%	two-channel monitoring device	[27]
	in women	21%		
	in men	40%		
	in men >70 years old	47%		
165	>15/h	32.7%	PSG	[28]
	>15/h in women	10.3%		
	>15/h in men	24.7%		
40	>5/h	77.5%	cardiorespiratory monitoring	[29]
	> 5/h central apnea	32.3%		

Treatment with continuous positive airway pressure (CPAP – a method of choice of treatment of OSA patients, preventing the occurrence of obstructive sleep breathing episodes) resulted in the improvement of insulin resistance and glycemic control in OSA patients with sub-optimally controlled t2D [38]. Improvement in insulin resistance in OSA patients during CPAP treatment has been confirmed in several studies [39, 40]. Recently, increase in insulin resistance after three months of CPAP treatment was found in OSA patients with EDS, but not in patients without EDS [37].

6. DIABETES AS A RISK FACTOR FOR SLEEP DISTURBANCES

On the other side, some typical symptoms of diabetes, such as peripheral neuropathy [41-49] and nocturia [50, 51] may influence sleep quality and quantity. Nocturia significantly worsens sleep quality [52, 53]. In patients' experience, nocturia has not only a negative influence on sleep quality and duration, but also on daytime cognitive functioning [54].

Similar effects may be a result of frequently associated with diabetes sleep movement disorders, such as restless legs syndrome (RLS) and periodic legs movements during sleep (PLMS) [55-59]. The assessment of sleep pattern and its length is recommended as a part of a comprehensive diabetes examination [60]. Fig. 1 illustrates the bidirectional influence of sleep and diabetes.

7. COGNITIVE IMPAIRMENT DURING DIABETES

Cognitive impairment is a frequent and important complication of diabetes and in some diabetic patients, dementia of various etiologies may develop. A recent meta-analysis confirmed the association between diabetes and increased risk of cognitive impairment and dementia [61]. Mild cognitive impairment occurs in 37.5% - 53% of t2D patients [62-64] and severe cognitive impairment in 16% of t2D patients [65]. In type 1 diabetes patients aged over 60 years, clinically important cognitive impairment was found in 48% [66].

The epidemiologic study based on 87 816 individuals aged 65 years or older with diabetes lasting for at least two years revealed that the risk of incidence of Alzheimer's disease (AD) and related syndromes was associated with poor diabetes monitoring and frequent diabetes complications [67]. The correlation between t2D and AD is complex. Common features characterizing t2D and AD are: insulin resistance, abnormal glucose metabolism in peripheral tissues, disturbed oxidative stress reactions, mitochondrial dysfunction, and insulin-mediated insulin transmission disorders, amyloid deposit aggregation, atrophy/neuronal degeneration and cognitive dysfunctions [68-74]. In diabetic patients with AD, hyperphosphorylation of tau protein, amyloid β (A β) deposition disorders, higher levels of IL-6 in cerebrospinal fluid and more frequent ischemic changes in the central nervous system (CNS) caused by small blood

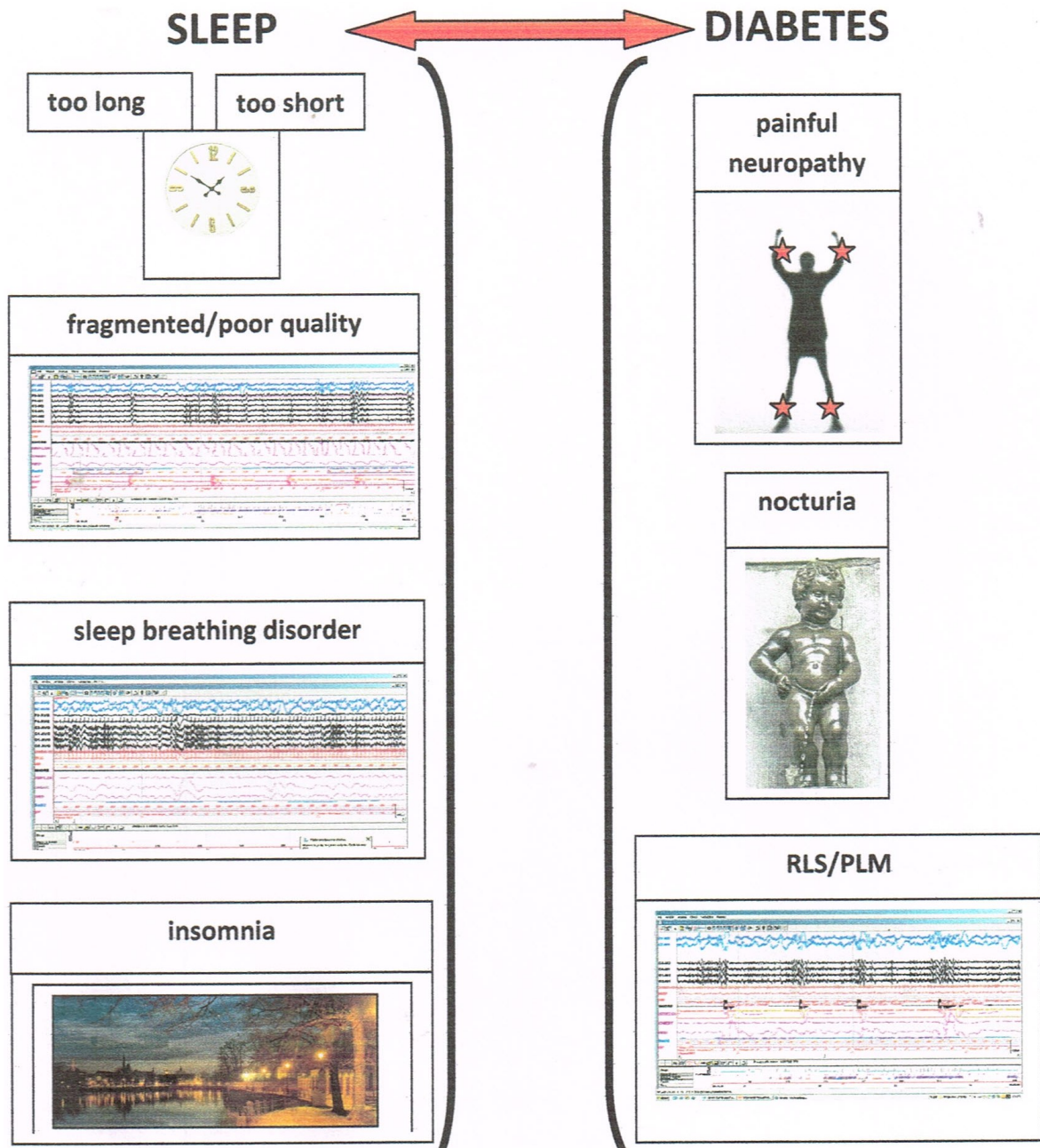


Fig. (1). Bidirectional influence of sleep and diabetes. Too long or too short sleep, as well as fragmented or poor quality sleep, insomnia or interrupted sleep and accompanied by hypoxemia in the course of sleep breathing disorder, may be associated with increased risk of diabetes. On the other side, however, diabetes may be associated with symptoms and signs that significantly interrupt sleep, such as painful polyneuropathy, nocturia or restless legs syndrome, which is frequently accompanied by periodic leg movements during sleep (RLS/PLM). The details on bidirectional influence of sleep and diabetes are discussed in the text. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

vessel pathology than in non-diabetic AD patients are observed [75-77]. Of the many factors common to AD and t2D, insulin resistance is the one that most likely underlies AD [78-80].

In a cohort study encompassing 10 316 diabetics and 41 264 non-diabetic adult patients matched by sex and age adjusted HR for dementia was 1.47, indicating a higher risk of severe cognitive impairment among diabetics [81]. In this study, the coexistence of hypertension, hyperlipidemia, or

both in the group of patients with diabetes did not further increase the risk of dementia. These findings indicated diabetes itself as the main cause of dementia risk. However, in the study encompassing 33 709 adult patients with diabetes and 67 066 patients without diabetes, matched by sex and age, observed for 10 years HR for dementia was 1.41 in the group of diabetic patients without hypertension, coronary artery disease, stroke, kidney disease or hyperlipidemia, and 2.49 in the group of the patients with at least four of these

comorbidities [82]. These data indicate a strong influence of vascular factors in the development of cognitive impairment in the course of diabetes.

The risk of development of cognitive impairment in diabetic patients may be related to non-vascular and vascular causes [83, 84].

7.1. Non-vascular Causes of Dementia in the Course of Diabetes

7.1.1. Hypoglycemia

One of the non-vascular mechanisms leading to cognitive impairment in the course of diabetes is hypoglycemia [66]. Studies conducted in animals indicate that mild/moderate hypoglycemia in a relapsing manner (as occurs in patients using insulin therapy) may lead to cognitive impairment. This is due to the special sensitivity of the hippocampus structures, responsible for memorizing. Repeated episodes of hypoglycaemia induce the activation of oxidative stress reactions, which, among others, underlies the damage of the CNS [85]. Severe hypoglycemia may be an important factor contributing to dementia, as shown by the study of 2001 diabetic patients. In the group of patients who previously experienced the episodes of severe hypoglycemia (3.1% of the patients studied) the risk of dementia was higher than in the remaining patients and in 1263 patients followed-up prospectively the risk of incident dementia associated with hypoglycemia HR was 2.54 [86]. In the hospitalized patients with type 1 diabetes and t2D, the individuals who have experienced episodes of hypoglycemia had poorer results in Mini-Mental State Examination than diabetic patients with no history of hypoglycemia [87]. However, the values close to the cut-off point, although differing statistically importantly, should be interpreted with caution. Animal studies allowed to find that recurrent mild hypoglycemia occurring in the course of the diabetes treatment might lead to cognitive impairment through mitochondrial and synapse injury [88].

7.1.2. Hyperglycemia

On the other side, however, poor diabetes control, with episodes of increased plasma glucose concentration may also lead to cognitive impairment. Hyperglycemia, often overlooked or neglected by patients due to the lack of spectacular clinical symptoms typical of hypoglycemia, is dangerous not only because of long-term complications due to, among the others, vascular disorders. It has also a direct negative impact on the CNS, contributing, inter alia to the slowing down of cognitive functions [89, 90] and it can also be associated with sleep disorders [91]. Imaging study revealed slower growth of the hippocampus associated with increased exposure to hyperglycemia and greater glycemic variability in children with type 1 diabetes [92]. The harmful effect of hyperglycemia is also visible at the cellular level, as high glucose releases the cytochrome c from the mitochondria to the cytoplasm, resulting in the activation of caspase 3 - a proapoptotic enzyme initiating a cascade of reactions leading to DNA fragmentation and cell death [93].

The meta-analysis of cognitive function studies in t2D revealed the association of higher HbA1c levels and deficits of processing speed and working memory/executive function

in t2D patients [94]. In children with type 1 diabetes, cognitive impairment is related to the level of glycemic control [95].

7.1.3. Central Insulin Resistance

Central insulin resistance, called by some authors type 3 diabetes (or called brain diabetes), leads to cognitive impairment [96]. Insulin and insulin-like growth factors (IGF-1 and IGF-2) are biologically active due to the stimulation of tyrosine kinase receptors – insulin receptor and insulin growth factor receptor (IGFR) [97]. These receptors are also found in the CNS with a different distribution. Immunohistochemical studies carried out on the brains of mice showed the highest expression of insulin receptor proteins in the olfactory bulb, cortex, hippocampus, hypothalamus and cerebellum with a low level of expression in the striatum, thalamus, midbrain and brainstem region; IGFR proteins showed the highest expression in the cortex, hippocampus, thalamus, moderate expression in the olfactory bulb, hypothalamus, cerebellum and the lowest expression level in the striatum, midbrain and brainstem [98]. Interestingly, different functions of central insulin receptors and IGFRs have also been demonstrated. Genetically modified mice lacking brain insulin receptors in the brain are characterized by normal development and size of the brain, suggesting that the presence of insulin receptors does not affect the survival of neurons. However, these mice developed metabolic abnormalities, such as increased appetite, obesity, insulin resistance, hypertriglyceridemia, and hyperleptinemia. In addition, fertility disorders were observed, probably related to insufficient gonadotrophin stimulation - hypothalamic-pituitary axis dysfunction in the secretion of luteinizing hormone [99].

Nowadays, insulin is thought to play an important role in cognitive processes [100]. Studies conducted in rats have shown improvement in cognitive function (memory consolidation) caused by intraventricular insulin administration after the task [101]. Memory improvement was also observed in patients with AD who developed hyperinsulinemia status through intravenous infusion [102]. However, to maintain a favorable cognitive effect, it is important to maintain a stable level of glycemia. Intraperitoneal administration of insulin in mice with no simultaneous supply of carbohydrates resulted in decreased cognitive ability; most likely, it was associated with the induction of hypoglycemia, because the simultaneous amount of insulin and glucose leveled the deficit to a degree proportional to the obtained glycemia [103-105]. The insulin supply used while maintaining normoglycemia resulted in an improvement of verbal memory and selectivity of attention [106]. Studies conducted in animals have demonstrated the beneficial effect of insulin in the prevention of secondary cognitive impairment as a consequence of ischemic stroke: In the brains of rats subjected to insulin therapy with maintaining euglycemia, the hypoperfusion-induced neuronal necrosis in the cornu Ammonis 1 (CA1) region of the hippocampus was reduced in comparison to the brains of animals in which only glucose infusions were used [107]. Insulin also suppressed the cognitive deficit caused by scopolamine [108], showing a beneficial effect on central adrenergic transmission.

The insulin receptors located in CNS do not function as a glucose uptake regulator as is the case in peripheral tissues. Glucose transporters (GLUTs), expressed on the surface of CNS cells, perform their functions independently of insulin. GLUT-1 is mainly found on the surface of astrocytes and cerebral vascular endothelium, while GLUT-3 expression is observed on neurons [109, 110]; both GLUT-1 and GLUT-3 are insulin-independent [111]. Central insulin receptors differ from their peripheral counterparts also at the molecular level - they show a lower molecular weight of the α and β subunits; this is due to alternative splicing of exon 11 mRNA and differences in the glycosylation of receptor proteins [112, 113]. Immunological changes are related to molecular differences - serum with anti-insulin antibodies, the administration of which blocked the binding of insulin to its peripheral receptor did not affect the ligand-receptor reaction in the CNS [114]. Insulin receptors play an important role in learning and memory by shaping synaptic connections due to the influence on glutamatergic and GABAergic transmissions [115, 116].

Insulin causes exocytosis of *N*-methyl-D-aspartate (NMDA) receptors on the surface of the cell membrane [117]. Because these receptors play important role in cognitive processes, enhancement of NMDA transmission seems to be one of the possible mechanisms underlying the central functions of insulin [118, 119]. Among the effects of insulin in CNS, *inter alia*, inhibition of A β secretion into extracellular space [120], protection against accumulation of hyperphosphorylated tau protein [121] and influence on brain neurotransmission through its effects on GABA-A receptors [122] are named. Insulin reduces the number of A β oligomers binding sites on the surface of neurons through a mechanism that uses insulin receptor tyrosine kinase activity [123]. A β disrupts insulin/IGF-I signaling; soluble deposits of A β oligomers result in a significant reduction in the number of membrane receptors of insulin on neurons [124].

It has been postulated that central insulin resistance plays an important role in the pathogenesis of AD [125-127]. The central insulin resistance found in AD is the result of molecular mechanisms similar to those that lead to peripheral insulin resistance in t2D. It progresses with age, as shown by molecular and clinical studies [128, 129]. Central insulin resistance is a distinct phenomenon that develops independently of peripheral insulin resistance [130, 131]. However, according to the metabolic hypothesis of AD, A β -mediated alterations in the hypothalamus may lead to peripheral metabolic dysregulation, while cerebral A β traversing the blood-brain barrier may affect peripheral tissues, contributing to peripheral insulin resistance [132].

The dysfunction of insulin receptor activity is caused by serine phosphorylation, resulting in a decrease in insulin receptor sensitivity [133]. The occurrence of such abnormal phosphorylated receptors has been confirmed in the brains of AD patients [134]. It has been shown that excessive phosphorylation occurs as a result of neuronal exposure to A β oligomers that stimulate the activity of c-Jun N-terminal kinases (JNKs), protein kinases dependent on double-

stranded RNA (PKR) and I κ B kinases (IKK) through pro-inflammatory activity - increase of TNF- α and other inflammatory cytokines. JNKs are over-activated by proinflammatory cytokines, such as (TNF- α) and free fatty acids (FFA), whose elevated concentrations have also been shown in the course of t2D [135]. Disorders of JNKs activity are probably the cause of axonal transport dysfunction occurring in the course of many neurodegenerative diseases, including AD [136]. It has been observed that insulin normalizes the activity of JNKs [134], perhaps the strengthening of its central action will have a positive effect on the course of AD. Central insulin resistance can precipitate the formation of pathologic lesions associated with AD, such as tau aggregates and amyloid plaques, and conversely, tau protein can influence the function of brain insulin and thus vicious circle may develop [137].

7.1.4. Other

Molecular consequences of carbohydrate metabolism disorders such as advanced glycation end products (AGEs) and their receptors (RAGEs) were found to take part in A β transport through blood-brain barrier. Administration of targeted RAGE inhibitor reduced A β influx across the blood-brain barrier and improved cognitive deficits in genetically modified mice by reduction of neurons' apoptosis and improvement of hippocampal plasticity [138]. Similar results considering the role of RAGEs in A β transport were obtained in human study, showing that AGEs induced A β transport by blood-brain barrier, increased expression of RAGE and nuclear factor-kappa B p65 (NF- κ B p65) and reduced nuclear peroxisome proliferator-activated receptor γ (PPAR γ) [139].

The hypothesis of the inflammatory basis of mild cognitive impairment in t2D patients has recently been supported by the study revealing the association of increased plasma IL-1 β levels with mild cognitive impairment, especially with memory impairment [63]. Animal studies suggest initial axon segment shortening in the prefrontal cortex and hippocampus as one of the factors associated with cognitive impairment in t2D [140]. Amylin - protein co-secreted with insulin - accumulates in the brain of AD patients and may interact with A β to exacerbate the neurodegenerative process [69].

Decreased levels of leptin were associated with cognitive impairment in 124 t2D patients, including 61 patients with mild cognitive impairment [141]. In the group of 138 patients with mild cognitive impairment in the course of t2D, the concentration of adiponectin was significantly lower than in the t2D patients without mild cognitive impairment and lower than in the healthy controls [64].

Decreased plasma ghrelin level was an independent factor of mild cognitive impairment in t2D patients ($p < 0.01$) [142]. In another study, however, there was no association between ghrelin concentration and Montreal Cognitive Assessment (MoCA) score in t2D patients, and the neuroprotective role of ghrelin has been postulated [143]. The association between plasminogen activator inhibitor 1 (PAI-1)

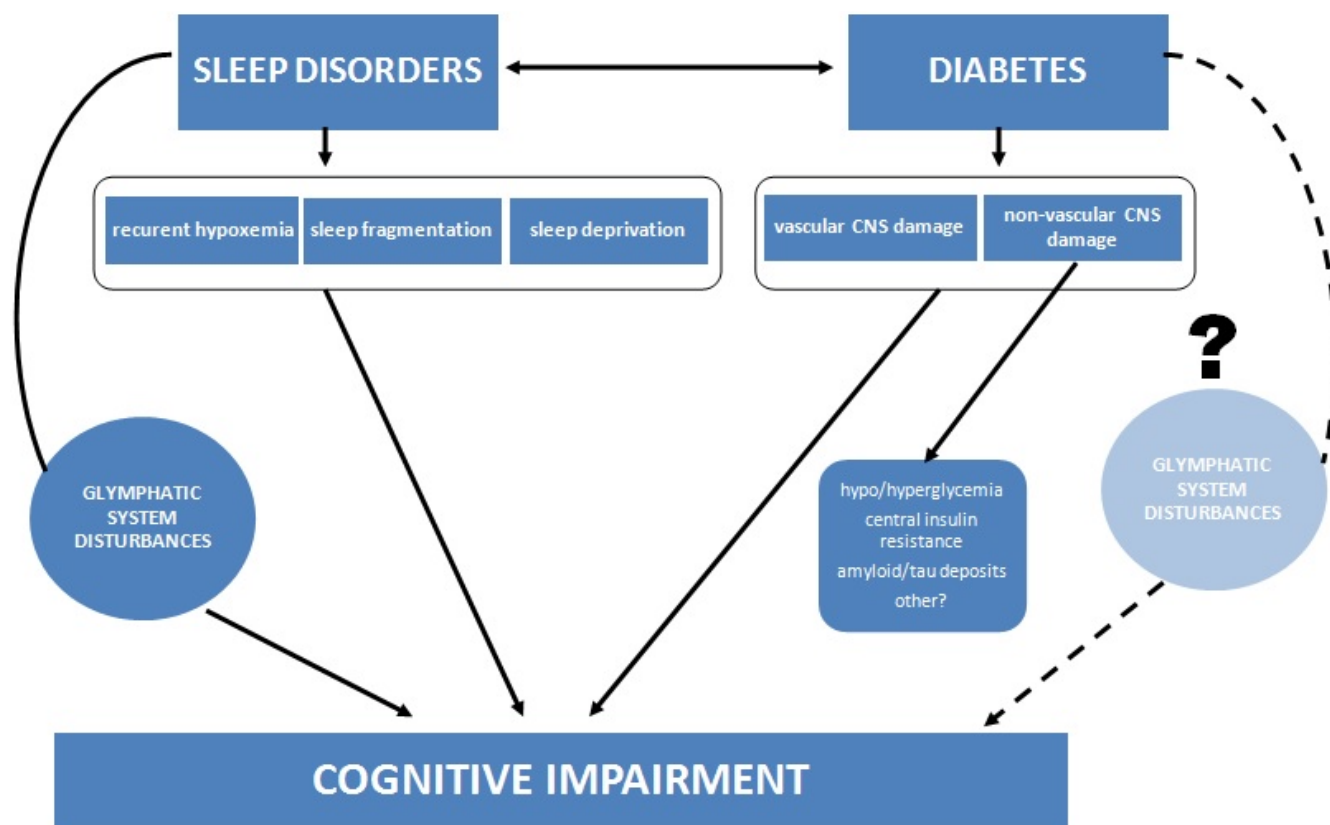


Fig. (2). Possible link between sleep disturbances, diabetes and cognitive impairment. Diabetes leads to cognitive impairment through - possibly - vascular and mostly non-vascular ways, such as hypo- or hyperglycemia, central insulin resistance, amyloid and tau deposits, hormonal mechanisms and the other. Both - although mostly sleep disorders and probably also independently diabetes - may impair glymphatic system functioning, thus leading to cognitive impairment and possibly to Alzheimer disease. The bidirectional relations between sleep disorders and diabetes are presented in the Fig. 1. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

and cognitive function in diabetic patients has recently been found: there was a significant negative correlation of PAI-1 concentrations and logic memory, as assessed by MoCA score in t2D patients with mild cognitive impairment ($r=-0.343$, $p<0.01$) [144].

7.2. Vascular Causes of Dementia in the Course of Diabetes

T2D is also a risk factor of vascular dementia [83]. Changes in the CNS in the course of diabetes may result from macro- and microangiopathies of blood vessels supplying the brain. Microvascular disorders, including CNS are common among diabetic patients and also have an effect on cognitive impairment in this group [145]. Chronic hyperglycemia, through the mechanism of microvascular dysfunction leads to dysregulation of cerebral processes and cognitive impairment [146, 147]. The areas of the brain associated with learning and memory - the hippocampus and the cerebral cortex, especially in the prefrontal region - are particularly sensitive to hypoxia. Diabetes may stimulate the development of AD by inducing vasculitis responsible for memory deficits and cognitive impairment, as shown in animal studies [148]. Although cognitive impairment in diabetic patients has frequently been associated with vascular abnormalities, one of the recent studies with the use of magnetic

resonance imaging has not revealed the association between small vessel disease score and cognitive function [149]. Impaired cognitive function in the course of diabetes, such as related to memory or executive function, may lead to significant functional decline [150] and is strongly associated with mortality risk (HR 2.72, 95% CI 1.48-5.01) [151].

8. SLEEP DISORDERS AND COGNITIVE IMPAIRMENT

Different sleep disorders, including sleep apnea, may lead to the progression of the development of neurodegenerative diseases [152]. There is a strong association between sleep disorders, including OSA syndrome, and AD [153]. The results of Pittsburgh compound B positron emission tomography scans indicate increased brain amyloid deposits in OSA patients [154]. Cognitive dysfunction is a common consequence of OSA [155]. Sleep disturbances in OSA syndrome lead to cognitive impairment in several psychological domains [156].

Insomnia is also associated with an increased risk of dementia [157]. The mechanism linking primary insomnia with cognitive decline is probably associated with increased deposition of A β the brain due to insufficient sleep time [158].

9. SLEEP DISTURBANCES, DIABETES, AND GLYMPHATIC SYSTEM FUNCTIONAL IMPAIRMENT

Several recent studies revealed the functioning of the central system of clearance of the brain from toxic substances, such as A β , called the glymphatic system [159]. The accumulation of A β leads to cognitive impairment [160]. Physiologic sleep is essential for adequate functioning of glymphatic system and thus sleep disorders may facilitate A β deposition in the brain leading – over the decades – to AD [161]. The study in animals revealed increased brain clearance related to sleep [162] and increase of A β in the brain after sleep deprivation [163, 164]. Similarly, in humans, there is decreased A β clearance with chronically decreased nocturnal sleep duration [165], as well as after one night of total sleep deprivation [166].

There is also an influence of diabetes on the glymphatic system [167]. The animal studies indicated the suppression of clearance of interstitial fluid in the hippocampus and hypothalamus. Thus a link between diabetes, disturbed function of glymphatic system and cognitive impairment has been suggested [168]. Fig. 2 illustrates the possible link between sleep disturbances, diabetes and cognitive impairment.

10. MANAGEMENT OF PATIENTS WITH SLEEP DISTURBANCES, DIABETES, AND COGNITIVE IMPAIRMENT

Identification of the relationship between sleep disturbance, diabetes and cognitive impairment must be considered in the efforts to identify potentially treatable and modifiable factors that may contribute to the development of cognitive impairment in older adults (Fig. 2).

Recognition that the etiology of sleep disturbances and cognitive impairment in diabetes is often multifactorial, which is essential to the successful evaluation and subsequent treatment of sleep disorders in old population. The differential diagnosis of sleep disorders in the older population should mainly include insomnia, sleep-disordered breathing, and restless legs syndrome/periodic legs movements during sleep.

Physicians should be aware that cognitive impairment is an important complication of sleep disorders, especially in pre-diabetic and diabetic patients. Cognitive assessment, *i.e.* screening and surveillance, should be an important part of the routine care of the older person with sleep disorders and pre-diabetes or diabetes. Unfortunately, the current management of older patients with sleep disorder and diabetes does not include routine assessment of cognitive function, and the cognitive function of the individual is not taken into consideration when devising a treatment plan.

CONCLUSION

The review of the current literature seems to indicate a mutual influence of sleep disturbances and diabetes that may be related to the cognitive impairment seen in patients with diabetes and sleep disorders.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
AGEs	=	Advanced glycation end products

AHI	=	Apnea/hypopnea index
A β	=	Amyloid β
CNS	=	Central nervous system
CPAP	=	Continuous positive airway pressure
EDS	=	Excessive daytime sleepiness
GLUTs	=	Glucose transporters
HOMA2-IR	=	Homeostatic model assessment of insulin resistance
IGF	=	Insulin-like growth factors
IGFR	=	Insulin growth factor receptor
IKK	=	I κ B kinases
JNKs	=	Jun N-terminal kinases
MoCA	=	Montreal cognitive assessment
NF- κ B p65	=	Nuclear factor-kappa B p65
NMDA	=	<i>N</i> -methyl-D-aspartate
OSA	=	Obstructive sleep apnea
PAI-1	=	Plasminogen activator inhibitor 1
PKR	=	Protein kinases dependent on double-stranded RNA
PLMS	=	Periodic legs movements during sleep
PPAR γ	=	Peroxisome proliferator-activated receptor γ
PSG	=	Polysomnography
PSQI	=	Pittsburgh Sleep Quality Index
RAGEs	=	Receptors of advanced glycation end products
RLS	=	Restless legs syndrome
t2D	=	Type 2 diabetes

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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