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Exploring Sleep Characterization, Causation, and Comorbidity in Sleep Disorders and Type II Diabetes Mellitus

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Abstract

Individually, diabetes and sleep disorders (SDs) have a detrimental impact on physical and emotional health. The concomitance of diabetes and SDs has also revealed a myriad of negative implications regarding general health and overall well-being. The extent and primacy of this relationship is elusive due to significant rates of inadequate or under diagnoses of SDs; as well as, the multitude of intervening variables that are associated with disease symptomatology. However, current research indicates that diabetes not only decreases sleep quality, but SDs may also augment the risk of developing diabetes. The multilateral nature of diabetes associated with SDs presents confounding variables and overlapping symptomatology that mediates disease pathogenesis. A literature review was conducted and data were collected from those with a SD and diabetes diagnosis compared to those diagnosed with a SD to elucidate sleep characterization, comorbidity, and a causal relationship. Recommendations regarding the challenges in daily self-management of diabetes associated with SDs are also identified. Comparison of both groups during NPS highlighted differences in sleeping efficiency and nocturnal hypoxemia, as well as contrasted the time spent in each sleep stage. Results also suggest SDs predispose a person to type II diabetes and comorbidities are clarified. It was revealed that those diagnosed with diabetes and a SD had a considerably higher incidence of other physiological and psychological conditions, including: depression, stress, elevated BMI, metabolic syndrome, hypertension, cardiovascular complications, lung disease, thyroid disease, sudden cardiac death, and stroke.

Keywords: Diabetes, sleep disorders, comorbidities, causal relationship

1. Introduction

Currently, there are over 1.5 million new diagnoses of type II diabetes in the United States per year.[9] Diagnosis of diabetes greatly mediates various aspects of health-related quality of life (HRQoL) for up to six years post-diagnosis.[36] This includes physical, social, and emotional aspects of health.[37] Despite improvements in diabetes management, diabetes is the leading cause of what is commonly referred to as, the big three: amputation, visual impairment and loss, and end-stage renal disease.[10]

Tantamount to this, nearly 70 million people in the United States experiences sleep disorders (SDs).[11] SDs are established to have various negative implications on individual health, and augment risk of: coronary event,[31, 61] weight gain,[73] obesity,[23, 31, 73] higher BMI,[1, 5, 39, 54] hypertension,[3, 6, 31] depression,[31] migraines,[12] and ADD/ADHD.[27] Similarly, SDs have demonstrated to greatly impact neuropsychological development and functioning.[19] Whereby, SDs mediate the ability to process sensory information and are associated with increased perceptions of pain.[8]

Diabetes and SDs are highly comorbid conditions that overlap in symptomatology, influence one another, and frequently occur together.[31, 39] A previously realized trend revealed that when the number of diabetes diagnoses increased, the number of average hours slept per night decreased in the United States.[25] Imperatively, it is recognized that of new diabetes diagnoses 50-55% may also experience reduced sleep quality or sleep disorders[14, 35] and up to 78% experience obstructive sleep apnea (OSA).[21] Indeed, the multilateral nature of diabetes in

concomitance with SDs presents distinct challenges in daily self-management of diabetes, as SDs have been shown to compromise cognition, psychological well-being, general health, and HRQoL. Still, in clinical practice most sleep complaints are not further investigated for SDs, especially when occurring with a chronic illness, despite current improvements in early diagnosis and management of SDs.[26]

Of further concern, the concurrence of diabetes and SDs is not only thought to exacerbate all symptomatology but may be causative.[32, 58, 77] That is, SDs may act catalytically to a diabetes diagnosis. Short sleep durations have been linked with low levels of serum leptin[54] and increased levels of ghrelin,[23, 77] increasing appetite satiety,[24] BMI,[1, 23, 54] and obesity[31] thus, augmenting the risk for type II diabetes mellitus. While it is not conclusive whether or not SDs can be used as an independent etiological predictor of diabetes-risk, the biochemical complications of the shared relationship are demonstrated.[55, 75]

Noticeably, SDs and diabetes have a significant impact on physical and emotional health but the extent and causation of this relationship is elusive. The diagnosis of diabetes and SDs presents confounding factors such as medication use, obesity, and overlapping symptomatology of disease pathology such as metabolic syndrome, hyperinsulinemia, impaired glucose tolerance, insulin resistance and dyslipidemia.[31] This review seeks to elucidate sleeping patterns, explore a causative relationship, describe comorbidity of SDs and type II diabetes and outline disease management considerations. As new diabetes diagnoses continue to rise it is imperative that this detrimental association is better understood to ensure preventive measures and superior treatment of diabetes.

2. Literature Review

To investigate the complex association between diabetes and SDs a search in PMC, Medline, Science Direct, and Google Scholar was done in February 2014. All papers containing the terms: 'Sleep disorders and comorbidity', 'Diabetes and comorbidity', 'Sleep duration and diabetes', and 'Sleep disorders and diabetes' in the title or abstract were identified. The table of contents was also screened for articles that may have not been identified by the keyword search as well as articles that were recommended by Science Direct. The abstracts of these studies (n=2422) were then inspected to determine whether they contained information about (I) relevant comorbidities of sleep disorders and type II diabetes, (II) causation of diabetes by sleep disorders or shortened sleep ($\leq$ 6 hours), if the (III) sleep studies reported were based on nocturnal polysomnography studies, or (IV) contained relevant information regarding disease-management. The author then reviewed 661 studies that were based on the criteria (I), (II), (III) and/or (IV) as defined above. After, 45 papers were deemed the most relevant based on information that was to be gathered. The following information was gathered: in each study data were recognized for those diagnosed with a SD or shortened sleep ($\leq$ 6 hours) and a diabetes diagnosis compared to those whom were solely diagnosed with a SD or shortened sleep ($\leq$ 6 hours), then the sleep characterization, causation, comorbidity and confounding variables were recorded for such studies.

3. Sleep Characterization

Studies that compared those with a diagnosed SD and those with both diagnoses of a SD and diabetes were identified. This was done to reveal patterns that establish specific sleep characterization for individuals experiencing a SD and diabetes. It was demonstrated that those with a SD and diabetes diagnosis had distinguished sleeping architecture to those with a SD diagnosis (Figure 1). A majority of studies identified within the literature search used self-reported data to diagnose or characterize sleep complications, or poor sleepers, rather than complete nocturnal polysomnography studies (NPS) and multiple sleep latency tests (MSLT). This restricted the amount of data that could be used due to the inherent ambiguous nature of the actual structure and acuteness of the SD being referenced. Furthermore, data of this type implies that sleep complications, and/or self-determined sleep disorders are consequence of diabetes alone. Whereby, sleep complications, or poor sleeping habits, act as a mild symptom of diabetes opposed to a distinct and separate diagnosis. The 2012 study conducted by Seibert did not base its SD characterization on self-reported data and the results demonstrated an overall exacerbation of symptomatology as well as differences in sleeping patterns.[62] A study conducted by Aronsohn and associates employed NPS in data collection and further helps to characterize sleeping patterns in those with a SD and diabetes diagnosis.[1]

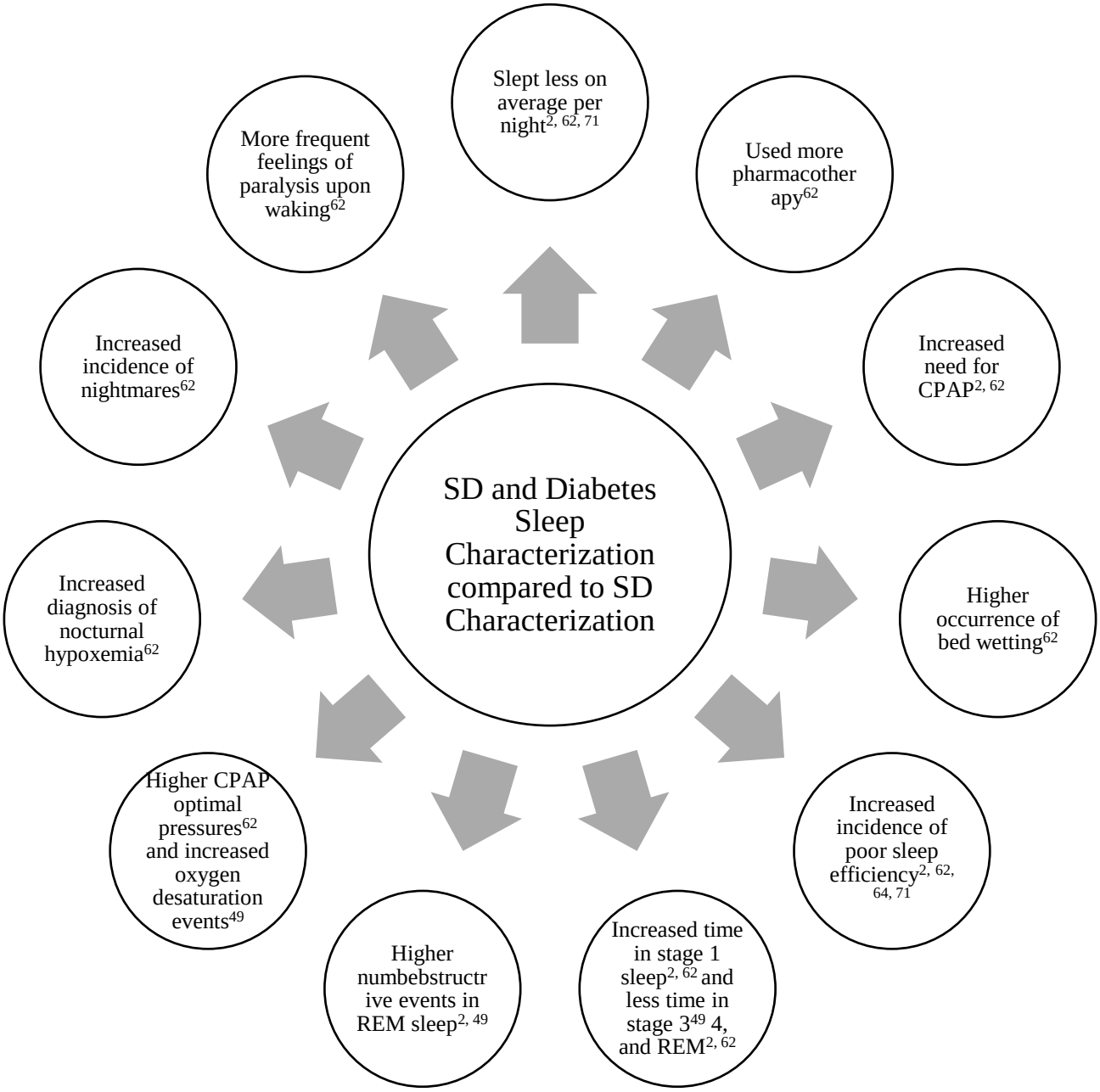

Figure 1. SD and diabetes sleep characterization compared to SD sleep characterization

4. Causation

Currently it is debated whether or not SDs can predispose a person to type II diabetes. Although it is agreed that decreased sleep duration mediates diabetes disease symptomatology, the mechanism for which this occurs and if it is causative is still widely studied. However, a mechanism for causation is proposed to be associated with hormone regulation, increased BMI and obesity, impaired glucose metabolism, and cytokine secretion (Figure 2). It should also be noted that this mechanism works in a pernicious cycle, wherein SDs predispose a person to type II diabetes and the diabetes worsens shared symptomatology such as metabolic syndrome and hypertension.[46] This, in turn, further reduces sleep duration, and exacerbates OSA disorders.[62] Conversely, studies identified have methodical

constraints. Wherein, sleep complications are self-reported, circadian rhythms are not measured, caloric variables are not adequately controlled, and there is insufficient data recorded for pre-diabetic or at-risk study populations in contrast to established diabetic populations.

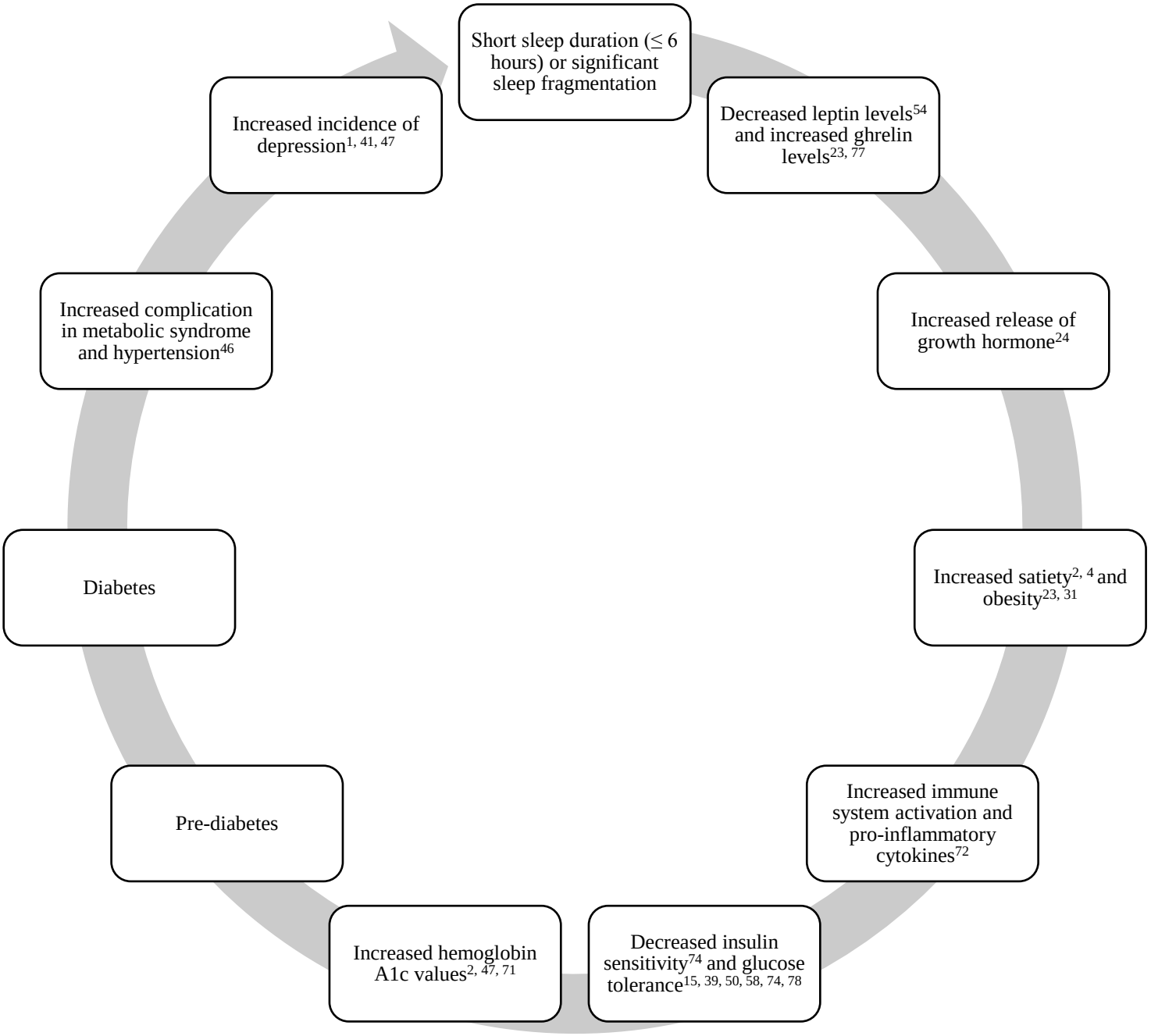

Figure 2. Pathogenesis of diabetes resultant from shortened sleep

5. Comorbidity

Similarly, it was found that concurrence of both diseases heavily increased relevant comorbidity. This included depression,[1, 41, 47] stress,[62] elevated BMI,[1, 47] metabolic syndrome,[48] hypertension,[47] cardiovascular complications,[18, 47, 65] lung disease,[62, 70] thyroid disease,[62] sudden cardiac death,[18] and stroke.[18]

Imperatively, such comorbidities as described above, in particular, metabolic syndrome, hypertension, and obesity mediate data which directly links OSA as an independent predictor of diabetes.[70] Accordingly, it has been shown that obesity is a bigger predictor of hyperleptinemia than OSA[57] and obese individuals with type II diabetes are at high risk for cardiovascular events[66] and developing OSA.[22, 66] Similarly, hypertension can occur in up to 50% of those with SDs and diabetes[14] and has been shown to individually reduce sleep efficiency, increase poor sleep quality, and increase risk of diabetes.[7] That is, obesity and hypertension are antecedent predispositions for SDs and diabetes individually, can independently result from SDs, and are also exacerbated when SDs and diabetes occur concomitantly. This comorbidity confounds data regarding causation and disease exacerbation proposed to be caused by SDs and diabetes, especially in regard to cardiovascular events.[18] Furthermore, a large population study (n=45,602) demonstrated that nonapnea sleep diseases may also predispose a person to type II diabetes development.[31] Still, participants had a BMI higher than average and reported comorbid conditions of hypertension, hyperlipidemia, stroke, cardiovascular disease, and depression, confounding data.[31] It should be noted that this was not the case for all participants and noncomorbid participants also demonstrated a heightened risk for developing diabetes.[33]

Of further significance, shortened sleep durations ($\leq$ 6 hours) have been shown to have an independent association with impaired glucose levels[40] and the concurrence of OSA and impaired glucose has further been implicated in worsening pancreatic beta-cell functioning, creating high-risk for diabetes development.[51] Moreover, it has been demonstrated in mice that lower levels of leptin are directly associated with deprived REM sleep independent of diet and sleep deprivation characterization, apnea or nonapnea.[57] Furthermore, there is current evidence revealing an independent association between OSA and glucose intolerance and insulin resistance, occurring independently of BMI.[52, 53, 74] According to Pamidi and associates this occurs in healthy men aged 18-30, with a BMI between 18 and 25 kg/m^2.[53] Other exclusion factors included: medications, depression, chronic or acute illness, and excessive smoking or consumption habits.[53] That is, obesity, cardiovascular disease, and pharmacotherapies may not mediate the etiology of type II diabetes from SD. Signifying that OSA is an independent cause of hormone abnormality and obesity which, in turn, predisposes an individual to diabetes. However, confounding factors in this shared relationship are frequently occurring and more research is needed in order to untangle the associated complex web of variables.

6. Management

Diabetes management requires a multidimensional approach. Decisions are made daily that impact treatment including: lifestyle changes, diet, exercise, medications, and self-management practices.[42] It is imperative that adequate and time sensitive treatment is attained for diabetes and SD management in order to facilitate superior patient outcomes. This includes reducing the occurrence of emotional distress[13, 43] further sleep complications or perceived poor sleep,[13] diabetes severity, and cardiovascular comorbidities.[43] It is imperative to note that treatment can be significantly mediated by poor physician-patient relationships and prevalence of comorbid conditions, resulting in non-compliant patients (Figure 3). Accordingly, reports as high of two-thirds of the diabetes population report inadequate management of disease, while half report significant impaired outcomes due to disease management.[63] Inadequate disease management and under diagnosis of diabetes and SDs, respectively, can be further linked to socioeconomic status, encompassing medical costs, and limited access to treatment. Wherein, people with the financial resources to afford health insurance are ten times as likely to pursue diabetes care as those who are underinsured, or cannot afford the cost of care.[43] Another hindrance in disease regulation is improper diagnostic tools for SDs.[56] Whereby, NPS and MSLT are not employed in SDs diagnosis. Consequentially, amplified disease progression and severity may be observed in clinical practice leading to higher incidences of cardiac events and morbidity.[18, 47, 66] Clearly, diabetes and SD self-care and treatment are a challenge with serious adverse consequences if inadequately addressed.

Continuous positive airway pressure (CPAP) has currently been demonstrated to treat SDs as well as enhance normal glucose levels, leptin and ghrelin hormone levels, as well as correct insulin resistance.[59] Still, CPAP presents

its own set of complications. This includes general discomfort coalesced with an individual's underestimation of their dire health needs, making it an inconsistent method of disease treatment.[59]

Presently, effective education is a useful self-management method and leads to positive disease outcomes.[13, 69, 76] However, knowledge is not always sufficient in maintaining adherence to self-care, diet, exercise, or pharmacotherapy regimes.[44] Successful patient-physician relationships are able to incorporate both education and support in order to promote necessary lifestyle changes and independence in self-care.[67] Fundamental behavioral modifications, such as depression and lack of motivation, can also be targeted by education strategies in order to facilitate optimal disease outcomes.[13] In this way, potential barriers are continuously recognized and appropriate behavioral and/or lifestyle modifications can be made as disease evolves throughout prognosis.

Emerging care for diabetes and SDs is primarily focused on the implementation of technology in management and treatment.[28] Specifically, studies have investigated the feasibility of telemedicine and telehealth in the treatment of chronic illnesses.[16, 29] Alluring qualities of telemedicine and telehealth include their ability to reduce healthcare costs for both patients and treatment facilities,[4, 34, 60] transcend geographical barriers that impede access to treatment,[17, 20] and promote consistent education.[16] It is thought that the incorporation of these novel technologies can reduce debilitating symptomatology associated with diabetes and SDs as well as increase independence in management of diabetes in particular.[16, 60] Despite technological advances and benefits of these systems full incorporation and implementation of telemedicine and telehealth has been a gradual process. Awareness and policy have not kept up with information technology.[30]

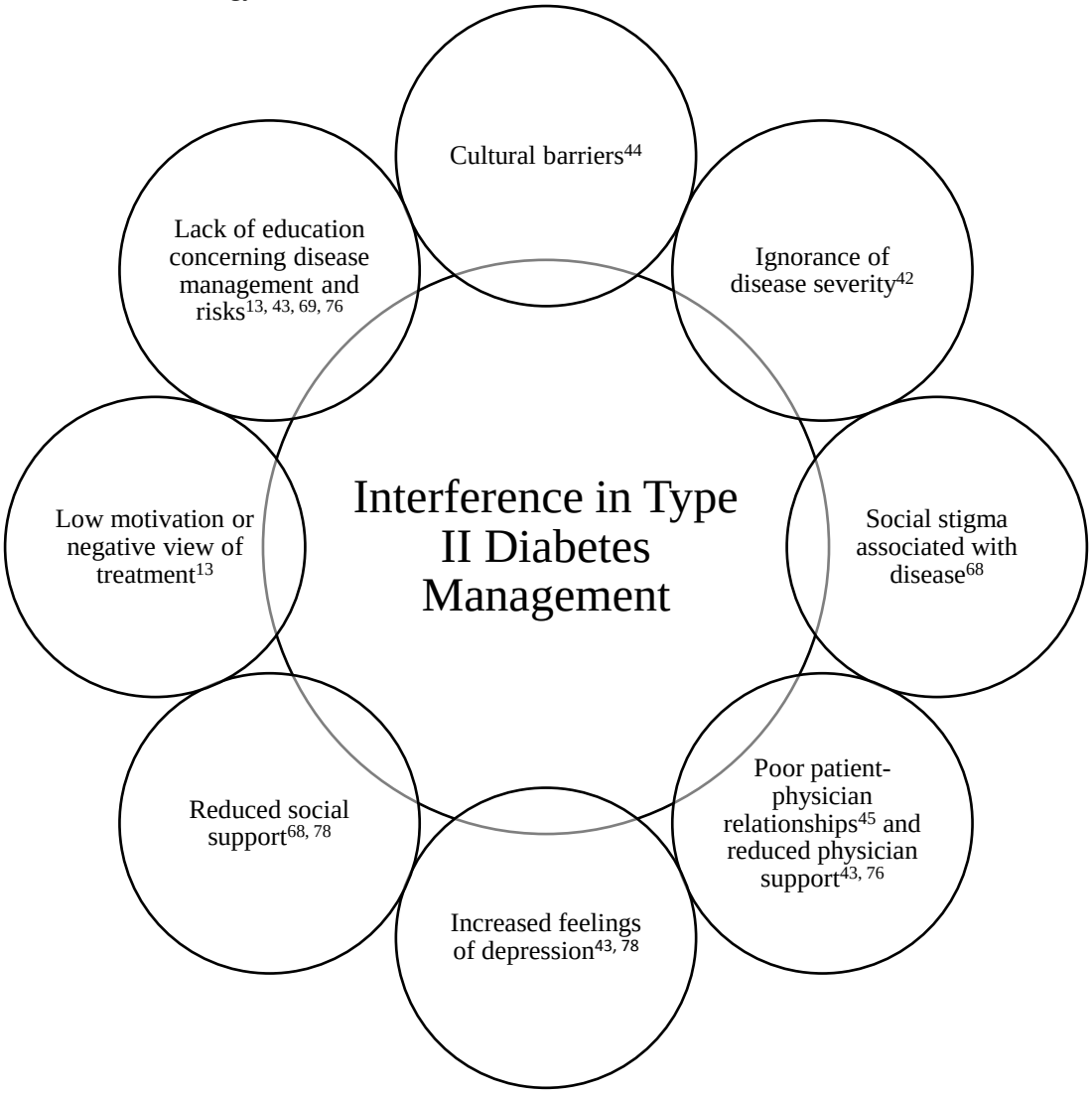

Figure 3. Notable interferences in diabetes management

7. Conclusion

This study highlights the differences in sleep characterization of the concomitance of SDs and type II diabetes compared to a SD diagnosis. Furthermore, it addresses the complications with sleep studies that base sleep disorders on self-reported data rather than diagnosis, NPS, and MSLT. There are a myriad of comorbidities presenting in diabetes associated with SDs. This supports previous research that has suggested frequent comorbidity is related to reduced sleep and diabetes. Comorbidity also mediates the linkage of SDs to the pathogenesis of type II diabetes. Therefore, a causal relationship cannot be definitively determined but the biochemical significance of the relationship is observed and a pernicious cycle of SD and diabetes pathology is outlined. Enhancing studies to include SDs based on NPS and MSLT, analyzing circadian rhythms, controlling and measuring caloric intake, confounding cardiometabolic factors, pharmacotherapies, and conducting longevity studies on at-risk, or pre-diabetes populations rather than diagnosed populations, is expected to further reveal relationships of primacy and causation.

Still, it is noted that this dual relationship is destructive by exacerbating all symptomatology and impeding disease management. Disease management can be challenging. Still, it is best attained through education, superior patient-physician relationships, and support networks. Moreover, novel technologies offer hope in reducing the costs of healthcare, eliminating barriers to treatment, and promoting continual education throughout prognosis.

Most concretely, this review demonstrates that sleep and diabetes have a powerful effect on individual health and overall well-being. This relationship mediates and exacerbates sleep quality, psychological and physiological symptomatology, and most significantly the health outcomes of an individual. This review proposes the existence of a detrimental association between SDs and diabetes that needs to be recognized in clinical practice and further researched in order to effectively manage disease and facilitate superior patient outcomes in disease progression.

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