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Relationship between sleep apnea and diabetes

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Background on Diabetes Mellitus

According to the American Diabetes Association, 8% of the general population and 25% of people over the age of 65 years are afflicted with diabetes in the United States and one of the most severe complications is the development of cardivascular disease[1-3]. Hyperglycemia has been shown to play a major role in the development of microvascular complications (retinopathy, nephropathy and neuropathy) and improvement of glycemic control can either prevent their development or slow their progression[4-7]. However, recent studies have clearly shown that intensive glycemic control has no meaningful impact of the development of macrovascular disease[4,8,9]. These studies strongly suggest that other factors that are associated with diabetes play a major role in the development of macrovascular disease in diabetes. The most prominent of these factors include dyslipidemia, hypertension, albuminuria, oxidative stress, nitrosative stress, accumulation of advanced glycation endproducts (AGEs)[10].

Most of the above factors contribute to the development of atherosclerosis[11] through the development of Inflammation and endothelial dysfunction[12-14]. Sleep apnea is also well known to be associated with endothelial dysfunction[15-17]. Thus, considerable progress has been made in delineating this relationship in rodent models of intermittent hypoxia by numerous different investigators[18-22]. However, there are very limited human data regarding the interaction between diabetes and sleep apnea in the development of cardiovascular disease. One recent report showed a very high prevalence of sleep apnea among obese patients with type II DM strongly suggesting that the OSA condition cannot be simply ignored in the DM literature[23]. In addition, even less data are available regarding the effects of sleep apnea treatment on the pro-inflammatory state and endothelial function of type 2 diabetic patients.

Diabetes also affects the microcirculation resulting to the development of long term complications, the most important of which are nephropathy, retinopathy and neuropathy. Studies in our unit and elsewhere have clearly shown the impairment of the skin microcirculation endothelium dependent and independent vasodilation in both the prediabetic and diabetic state[24-26]. Furthermore, additional studies that are presented in the preliminary data section indicate that sleep apnea may affect the resting skin

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blood flow and the maximal vasodilatory response after the iontophoresis of acetylcholine, that induces endothelium dependent vasodilation and sodium nitroprusside that induces endothelium independent vasodilation, probably as a result of increased sympathoexcitation. As there are currently very limited, if any, data regarding effects of sleep apnea on the microcirculation and its possible synergistic effects with diabetes, we believe that this field needs further exploration.

Protein Tyrosine Phosphatase 1B (PTP1B) in Diabetes

PTP1B is a ubiquitously expressed phosphatase that localizes predominantly to the endoplasmic reticulum[27]. Intense research over the last decade has shown that PTP1B negatively regulates the signaling of insulin and leptin resulting in insulin resistance[28-30]. In addition, PTP1B also affects the signaling of various growth factors including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor-beta (TGFβ) and platelet derived growth factor (PDGF)[31-33]. Recent studies have shown that inflammation induces the expression of PTP1B through the action of tumor necrosis factor a (TNFa) that leads to nuclear factor kB (NFkB) activation[28,29]. Due to PTP1B's key roles regulating insulin and leptin action *in vivo*, PTP1B inhibitor development is an active research area. PTP1B inhibitors are currently in stage 2 clinical trials for treatment of type 2 diabetes and obesity[34,35].

There are currently no data available regarding the role of pro-inflammatory conditions, such as sleep apnea, on the expression/activity of PTP1B. However, the possibility that sleep apnea-related inflammation causes increased PTP1B expression/activity that leads to insulin resistance and cardiovascular disease seems plausible and needs further investigation. Although we recognize that multiple pathways are important in the biology of these diseases, we have chosen to have a major focus on PTP1B for the following reasons. First, as mentioned above, numerous mechanistic animal studies have shown that proinflammatory conditions can raise the expression of PTP1B and cause insulin resistance. Second, our preliminary data clearly indicate that PTP1B is overexpressed in type II diabetes and may be related to the observed resistance of various growth factors that are involved in neuropathic wound healing. We are unaware of other groups who have focused on this pathway in the context of the interactions of OSA and DM. Thus, our studies will be novel. Finally, we do plan to explore other pathways in the context of this research, but have focused on our PTP1B hypothesis for this application. We recognize that our secondary hypotheses on cytokines and oxidative stress will be exploratory, but may provide data to help design subsequent studies.

Background on Importance of OSA

OSA is a common disease with major neurocognitive and cardiovascular sequelae[36]. Although the commonly cited statistics are that 4% of middle aged North American men and 2% of North American women have symptomatic OSA[37,38], these figures are likely underestimates. When these prevalence data were published in 1993, the prevalence of obesity was considerably less than it is today[39]. Because obesity is a major risk factor for OSA, the prevalence of OSA is likely to be increasing during the obesity pandemic[40]. In addition, the current use of nasal pressure technology to detect respiratory abnormalities is considerably more sensitive than the previously used thermistors[41, 42], which only detect fairly marked changes in air temperature. Thus, important respiratory events were likely missed in the 1993 study. Finally, the definition of "symptomatic" was based on the Epworth Sleepiness Score >10/24. However, considerable data now suggest that important sleep apnea can still occur without an elevated Epworth Sleepiness Score[43]. For example, OSA patients with a low Epworth Score may be at risk of cardiovascular consequences[44] and/or may have other symptoms such as non-restorative sleep, fatigue, difficulty concentrating etc[45-49]. Thus, limiting the definition of OSA based on Epworth Score alone is likely inappropriate. Regardless of the exact definition, OSA is highly prevalent and has important consequences.

The consequences of OSA are also now well established[50-58]. Some authors had previously suggested that OSA *per se* was not an important contributor to disease but was simply a marker of an unhealthy individual whose complications were a result of the associated risk factors (e.g. obesity, diabetes, alcohol, tobacco, hypertension etc.)[59] However, over the past decade, rigorous research has been performed which has clearly established the importance of OSA itself. In the neurocognitive area, numerous studies have shown benefits to

OSA treatment from standpoint of sleepiness, motor vehicle accident risk, and quality of life[45-47,49,60]. In the cardiovascular arena, a causal link between OSA and hypertension has now been established based on animal studies[61], large cross-sectional investigations[62], longitudinal epidemiological studies[63] and human interventional studies[64]. In an elegant model of OSA in dogs, Brooks *et al*. demonstrated that repetitive induced apnea led to systemic elevations in blood pressure during the daytime, which were then reversible with withdrawal of the apnea[61]. The Brooks study definitively showed a causal link between the induction of OSA and development of systemic hypertension independent of all known covariates. A number of authors including Lavie and Nieto have demonstrated robust associations between OSA and systemic hypertension independent of known confounding variables[62,65]. In the Lavie study the link between OSA and hypertension was stronger than for obesity with hypertension. In a longitudinal assessment of the Wisconsin Sleep Cohort, Peppard *et al.* demonstrated an increased *incidence* of hypertension among patients with sleep apnea as compared to controls[63]. Patients with even moderate sleep apnea had a tripling of the incidence of hypertension over the course of four years as compared to matched controls, independent of known confounding variables. Most recently, a number of interventional studies have revealed reductions in blood pressure with CPAP therapy as compared with placebo. Although the magnitude of reduction in these studies has been quite variable, the bulk of the evidence suggests important blood pressure benefits to CPAP therapy. In addition to hypertension, several studies have recently found a strong link between OSA and incident stroke[66,67]. OSA may also increase the risk of myocardial infarction and congestive heart failure, with some data supporting long term cardiovascular benefits to patients adherent with CPAP[68]. In summary, OSA clearly has neurocognitive and cardiovascular sequelae with the preponderance of evidence showing benefits to nasal CPAP therapy for afflicted individuals, particularly when adherent to treatment.

Because the OSA field was initially met with skepticism, investigators have gone to considerable lengths to isolate the independent effects of OSA on various outcome measures. As a result the OSA literature has largely overlooked or excluded the influences of the various associated disease states. In other words, DM has been considered a confounding variable rather than an important contributor (or effect modifier) for OSA-related disease risk. Thus, major contributions have been made in the study of the links between OSA and DM[21,69-71], but there has been minimal research regarding how these diseases interact from standpoint of vascular complications. That is, patients with diabetes were excluded from some of the critical OSA studies regarding vascular risk.

One could potentially argue that sleep apnea now has proven importance, and thus further research into the impact of OSA is no longer required. That is, showing CPAP improves vascular risk in DM patients may theoretically not change management since OSA should be treated regardless. However, we strongly believe that further investigation is justified. The majority of sleep apnea in the population remains undiagnosed, possibly due to a lack of appreciation for the importance of this condition among doctors and patients. Even among those who are diagnosed with OSA, enthusiasm for therapy is quite variable among those afflicted as well as practitioners. Since the bulk of the proven benefit for CPAP therapy in meta-analyses is based on sleepiness symptoms, the treatment of non-sleepy patients remains quite controversial. Studies suggest that the magnitude of the daytime blood pressure improvement with CPAP therapy is on the order of only 2-3 mmHg leading some to question the utility of this intervention to reduce vascular risk. Available data regarding benefits to CPAP therapy in terms of vascular risk come largely from observational cohort studies (e.g. Marin Lancet 2005[68]) which are highly confounded by healthy participant effects i.e. CPAP adherent patients are quite different from non-adherent ones in terms of education, motivation, adherence to medical therapy, diet, exercise etc. Thus, the rigorous demonstration that CPAP can reduce vascular risk among DM patients is likely to have a profound impact on the awareness of the OSA problem among people with DM, to improve motivation of patients and physicians to diagnose and treat apnea, and to fuel a discussion regarding non-pharmacological therapies in DM.

Relationship Between Sleep Apnea and Diabetes

There are a number of factors which link OSA to DM. First, obesity, as stated, is a major risk fa-

ctor for both DM and OSA and thus all three conditions are very common with increasing prevalence. Second, sleep apnea has been associated with DM[72]. A number of counter-regulatory hormones are released with each respiratory event, and therefore, one would logically predict that that intermittent hypoxia and ongoing respiratory events should drive up blood sugars[9,20]. Indeed, multiple cross-sectional studies have shown associations between OSA and hyperglycemia, independent of known covariates. However, the majority of interventional studies have not shown major improvement in glycemic control with CPAP therapy in OSA. The reasons for this discrepancy are unclear, but may reflect residual confounding in the association studies or poor adherence in the CPAP studies. Third, DM is associated with OSA. Both type I and type II DM have been suggested to be risk factors for OSA. The mechanisms underlying this association are unclear, but may reflect neuromyopathy in the upper airway[73,74]. However, these mechanisms remain controversial[75,76]. Fourth, sleep deprivation has been linked in epidemiological studies with poor outcomes including incident myocardial infarction, incident diabetes, and incident weight gain[77,8]. Some physiological studies have suggested that induced sleep deprivation can lead to reduced leptin and increased ghrelin concentrations, both of which would be predicted to stimulate appetite[79-81]. The ratio of leptin/ghrelin was in fact predictive of hunger/appetite in this study. Fifth, and of major importance to the present application, both OSA and DM are major risk factors for vascular disease. Both OSA and DM have been causally linked to oxidative stress and endothelial dysfunction[10,82,83]. Both diseases are major risk factors for myocardial infarction and stroke. However, minimal research has been performed examining the interactive vascular risk in patients with both DM and OSA.

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