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Is nitric oxide missing link in glucose homeostasis? A study on correlation of nitric oxide and insulin resistance in obstructive sleep apnoea

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ABSTRACT

Nitric oxide is associated with glucose homeostasis. An independent relationship between Nitric oxide and insulin resistance in Prediabetic and Obstructive sleep apnea patients without pre-existing diabetes mellitus are equivocally linked to increased risk of type II diabetes. A reciprocal relationship seems to exist between nitric oxide and insulin resistance. Aim of this present study is to determine relationship between nitric oxide and glucose parameters in control, prediabetic and Obstructive sleep apnea. A cross sectional study was performed in 150. They were divided into, group I (control), group II (prediabetics) and group III (OSA). Fasting blood sugar (FBS), fasting insulin, HbA1c and nitric oxide were measured in these subjects and insulin resistance calculated by HOMA-IR. Data was analyzed statistically using Pearson's correlation coefficient analysis, the significant value being P<0.05. Negative correlation was observed between the NO and insulin resistance in prediabetic (r=-0.627, P =<0.001) and OSA (r= -0.416, P=0.003) respectively. Nitric oxide is significantly inversely associated with insulin resistance in Prediabetic and Obstructive sleep apnea.

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INTRODUCTION

Nitric Oxide (NO), a potent vascular relaxing factor involved in regulation of various functions namely vascular tone regulation, inflammation and neurotransmission among other functions. Nitric oxide (NO) is synthesized from the amino acid L-arginine by the enzyme nitric oxide synthase (NOS). Three types of NOS are present; neuronal NOS (nNOS) in nerve cells, inducible NOS (iNOS) in inflammatory cells and endothelial NOS (eNOS) from endothelial cells (Förstermann *et al.,* 2012). The main Site of NO synthesis is the endothelium but it also produced in every tissue and organ of the body, from muscles to brain. NO is an important signalling molecule but high concentrations can be toxic and it has both paracrine and autocrine effects. NO in physiological amounts is beneficial to the cell. Decreased NO availability leads to a number of features of diabetes and might be an important molecular mechanism underlying the development of insulin resistance (IR) (Kashyap *et al.,* 2005). The redox balance in the cell is disturbed by many factors like hyperglycemia, increased adiposity, and dysfunction of the PI3K-Akt pathway and the resulting low NO production leads to increased insulin resistance. A reciprocal relationship exist between NO and IR. NO might act as a regulatory factor for the downstream signaling molecules linking GLUT4 translocation and glucose uptake, but action of nitric oxide in glucose uptake still remains unclear. (Kobayashi J *et al.,* 2015).

In Obstructive sleep apnea (OSA) characterized by frequent episodes of reduction in airflow or due to the obstruction in the upper air pathway of an individual resulted in intermediate hypoxia (Punjabi *et al.,* 2002) . Bioavailability of NO is reduced due to hypoxia, hypoxia–reoxygenation, shear stress, and ischemia reperfusion of the vascular wall. The decreased bioavailability of NO increases the occurrence of vascular morbidities such as hypertension, myocardial infarction and diabetes. Even though the association of serum NO and insulin levels remains debatable. Since there is a very close link between OSA and IR, investigations support this link by showing that other diseases like metabolic syndrome, diabetes, PCOD characterized by IR are also linked with OSA (Kent *et al.,* 2015) (Vgontzas AN *et al.,* 2001). The oxidative stress induces adaptive pathways, including altered nitric oxide bioavailability, increased lipid peroxidation, and up-regulation of nuclear factor B and hypoxia inducible factor alpha 1. Oxidative stress plays important role in the mechanism for insulin resistance and the onset of prediabetes and Type 2 diabetes (Giacco *et al.,* 2010). The contribution of specific pathways involved in hypoxia induced alterations in glucose homeostasis in OSA patients remains to be investigated. This study evaluates the relationship between serum nitric oxide and insulin resistance in control, prediabetic and OSA patients.

OBJECTIVE

To find correlation between NO and insulin resistance in control, prediabetics and Obstructive sleep apnea groups.

MATERIALS AND METHODS

A total of 150 patients in three different groups, normal, prediabetic and obstructive sleep were the subjects of this study, carried out in Department of Physiology, ACS Medical College and Hospitals, Dr. MGR Educational and Research Institute University, and Saveetha Institute of Medical and Technical Sciences, both in Chennai, Tamil Nadu, India, during January 2015–December 2016. This study was approved by Institutional Human Ethical Committee, Saveetha University - IHEC No-008/12/201/IEC/SU, Dated -18th December 2014, Chennai, Tamil Nadu. Written informed consent was obtained from all the participants.

Study Population: Adults who satisfied the inclusion criteria, were classified into three groups.

Group 1 – Normal, **Group 2** -Prediabetics, **Group 3** – Obstructive sleep apnoea.

The participants of Group I were selected from normal healthy population. Group II subject selection was based on their blood glucose level criteria for Pre-diabetics which are HbA1C of 5.7% – 6.4%, Fasting blood glucose of 100 – 125 mg/dl or OGTT 2 hour blood glucose of 140 – 199 mg /dl. Group III included obstructive sleep apnea patients who were newly diagnosed based on the polysomnogram (PSG), which remains the "gold standard" diagnostic tool. OSA was assessed by a single overnight cardiorespiratory sleep study using a four channel recorder and scored in accordance with the American Academy of Sleep Medicine.

Exclusion criteria: cardiac disease, hypertension, asthma, chronic obstructive pulmonary disease, liver disease, cancer, renal disease, active tuberculosis, and endocrine disorders such as diabetes mellitus (DM), Cushing's syndrome, and thyroid dysfunction. People with anatomical deformities such as craniofacial abnormalities and congenital cardiopulmonary disorders were excluded from the study.

Blood sample: The data collection procedure included collection of 5ml of peripheral blood in test tubes for biochemical analysis. Blood sample collected after overnight fast from all patients was used to study fasting blood sugar was estimated by GOD–POD method, glycated haemoglobin (HbA1C) by semi-automated analyzer (Erba Mannheim Transasia, Germany), fasting insulin by enzymelinked immunosorbent assay method by an automated analyzer (Evolis BIORAD, France) and insulin resistance was calculated by Homeostatic model assessment insulin resistance (HOMA-IR) by the formula - Fasting insulin (μIU/ml) x Fasting glucose (mg/dl) / 405. Estimation of nitric oxide was done by the standard method of Griess reagent, calorimetric method by using ultraviolet (UV) -visible spectrophotometer (UV-1601, Shimadzu).

STATISTICAL ANALYSIS

Correlations between blood levels of fasting glucose, fasting insulin, HbA1c and insulin resistance against blood nitric oxide levels were calculated by Pearson's correlation coefficient analysis for all three study groups. SPSS statistical software of version 9.0 was used for the analysis. Statistical significance was considered if the p – value was less than 0.05.

RESULTS

Correlation coefficient (r) and p value for control group fasting glucose level was $r_{=}0.057$ (p=0.692),

Table 1: Correlation between nitric oxide (NO) and glucose parameters in pre-diabetes, OSA and control groups

Glucose parameter	Control		Pre-Diabetes		OSA	
	r	p-Value	r	p-Value	r	p-Value
Fasting Glucose	0.057	0.692	-0.345	0.014*	-0.149	0.302
Fasting Insulin	0.112	0.439	-0.650	<0.001**	-0.436	0.002**
HbA1c	-0.076	0.600	-0.289	0.042*	0.130	0.367

* significant; **Highly significant

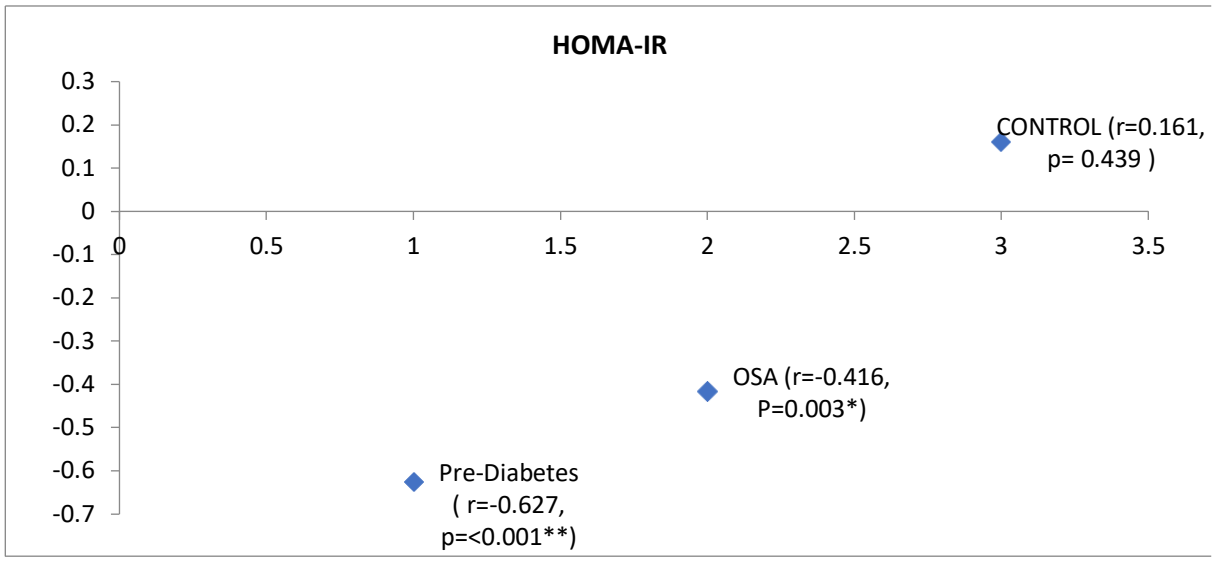

Figure 1: Correlation between nitric oxide (NO) and Insulin resistance in prediabetes, OSA and control groups

fasting insulin level r= 0.112 (p = 0.439), HbA1c r= -0.076 (P=0.600) and HOMA-IR r=0.161 (p = 0.263).

In prediabetic group the values were fasting glucose level r= -0.345 (p= 0.014), fasting insulin level r=0.650 (P<0.001), HbA1c r= -0.289 and HOMA-IR r= -0.627 (P= <0.001). Negative correlation was observed between NO and all measured parameters in prediabetic group.

In OSA group the values were fasting glucose level r=-0.149 (P=0.302), fasting insulin level r= -0.436 (P=0.002), HbA1c r= -0.130 (P = 0.367) and HOMA-IR r= -0.416 (P = 0.003). Negative correlation was observed between NO and fasting insulin and insulin resistance in OSA group.

DISCUSSION

Insulin resistance (IR) is the reduced responsiveness of target tissues (mainly skeletal muscle, liver and adipose tissue) to insulin. Obesity and insulin resistance are common features of type2 diabetes, metabolic syndrome and obstructive sleep apnoea. In IR, the biological response to normal concentration of circulating insulin is decreased. It is present for a period before development of overt type 2 diabetes (Guilherme *et al.,* 2008). Insulin mainly acts on carbohydrate and lipid metabolism, and also influences protein and mineral metabolism. It is the most powerful regulator of metabolic actions; its metabolic effects are responsible for energy storage in liver, muscle, and adipose tissue (Pessin JE *et al.,* 2000).

Insulin is the only hormone which reduces blood glucose level and is most essential for glucose homeostasis. Peripheral utilization of glucose in many cells including skeletal muscle is promoted by insulin (Lundberg JO *et al.,* 2009).Insulin combining to its receptor in insulin sensitive cells activates a variety of intracellular responses. It causes activation of two separate and parallel pathways: (i) PI3K–Akt and (ii) Ras/Raf/MAP kinase. In the PI3K–Akt pathway, insulin receptor substrate 1 (IRS1) is activated and it phosphorylates Akt which brings about two effects. The first is translocation of intracellular GLUT4 to the cell membrane which promotes entry of glucose into the cell; the second is stimulation of eNOS to produce NO which has a number of beneficial effects. The Ras/Raf/MAP kinase pathway leads to vasoconstriction and cell proliferation (Jun Kobayashi2015).

When intracellular energy levels are low, cellular metabolism shifts from anabolic processes to catabolic processes, favouring energy-consuming processes to energy-producing processes. AMPK is a sensor of intracellular energy status, it is

responsible for the switch from anabolism to catabolism. AMPK inhibits insulin-stimulated anabolic processes like lipogenesis and glycogen synthesis, but maintains glucose homeostasis and increase insulin sensitivity by promoting processes of glucose uptake and energy expenditure (Schultze et al 2012).

NO is a key signalling molecule throughout the body, and has multiple roles in immunity, smooth muscle contraction, peristalsis, mucus and gastric acid secretion, respiratory function, ATP utilization, and mitochondrial biogenesis. NO also has a major action in insulin signalling. NO penetrates the smooth muscles and acts as a vasodilator, which relaxes the blood vessels and help in glucose uptake. Low NO levels can cause hypertension, increased risk of cardiac vascular disease, dementia, neurodegenerative disorders and diabetes.

Some reports suggest the presence of increased circulating NO in insulin-resistance whereas others suggest that NO synthesis is reduced in the IR state (Sangeeta R. Kashyap *et al.,* 2005). The current study found negative correlation between nitric oxide and Insulin Resistance in both prediabetic and Obstructive Sleep Apnoea patients.

Studies by Schulz *et al.,* 2000 stated that NO levels are reduced in OSA and can be increased by short CPAP therapy. A recent study showed decreased eNOS activity accompanied by nitric oxide degradation in OSA patient and confirms that NO bioavailablity is decreased in OSA conditions (Atkeson 2008).The association between OSA and altered glucose metabolism has been shown in many studies, Makino et al in cross sectional study in 213 Japanese patients with OSA found that insulin resistance was independently associated with the severity of OSA. Peltier et al in 24 OSA patients found that 79.2% of patients with OSA had impaired glucose tolerance and 25.0% had previously undiagnosed type 2 diabetes. Einhorn D et al 2007 have shown no significant correlation between OSA and HbA1c in 279 diabetic patients. This result is supporting present study.

Negative correlation between NO and glucose parameters in prediabetic group is observed in this study. In prediabetes, blood glucose level is higher than normal, but not to the magnitude to be considered as diabetes. Oxidative stress and inflammation play an important role in the aetiology of prediabetes. Ozcelik et al in 2017 state that higher level of serum glucose, insulin and insulin resistance may be responsible for activation of endothelial cell resulting in increased NO levels in prediabetic. Markus P. Schneider et al in 2013 stated that poor glycemic control is related to higher NO activity in 113 patients with type 2 diabetes. But in contrast other studies show decrease of NO in type 2 diabetics. This contradiction may be related to the duration of prediabetes /diabetes. Initially, endothelium produces higher amount of NO to protect from inflammation and oxidative stress; but later, exhaustion occurs as a consequence of disease and results in decrease of NO. This is the reason for reduction of NO in later stages of diabetes. (Dara Kutsyk *et al.,* 2017). NO and insulin resistance have a reciprocal relationship; NO suppresses IR and reduction in NO leads to increased IR.NO might act as a regulatory factor for the downstream signaling molecules linking GLUT4 translocation and glucose uptake (Kim J *et al.,* 2006).

The molecular mechanisms involved in the AMP-activated protein kinase (AMPK) pathway that regulates cellular metabolism and activate glucose transport during hypoxia are relevant to the present study. AMPK is activated in response to a variety of stimuli, including cellular stress, exercise and hypoxic stress. Genetic and pharmacological studies have shown that AMPK is required for maintaining glucose homeostasis (Schultze et., 2012). Alternative pathways that influence glucose homeostasis induced by hypoxia in OSA patients remain to be investigated.

A number of physiological processes have been shown to stimulate AMPK pathway in hypoxia (Mu J *et al.,* 2011). Pharmacological activation of AMPK by drugs like Metformin mainly activate AMPK in the liver, muscle and vasculature promoting glucose uptake, fatty acid oxidation, biogenesis of mitochondria, and increasing insulin sensitivity; these processes are reduced in obesity and result in the development of insulin resistance (Hawley, S.A. *et al.,* 2002) (O Neill HM 2013). The activation of AMPK causes an increase in glucose transport in muscle by a mechanism involving phosphorylation of NOS and increased NO production (Chen Zp *et al.,* 1999). AMPK causes an increase in glucose transport via a NOS- and guanylate cyclase-dependent mechanism. Therefore, AMPK could increase glucose transport in muscle by increasing NO production via phosphorylation and activation of NOS with GMP as intermediary protein (Fryer *et al.,* 2000). The action of insulin is vasodilatation in skeletal muscle, which leads to increased blood flow that further enhances glucose uptake in skeletal muscle by nitric oxide (NO) produced from vascular endothelium in healthy conditions (Kim *et al.,* 2005). Hypoxia associated with OSA could lead to decreased nitric oxide production (Ip MS *et al.,* 2000). Low levels of NO can be the cause of dysfunction in downstream of the AMPK pathway in hypoxia and can lead to IR. Therefore, Nitric oxide may be the missing link in AMPK induced

pathway in altered glucose homeostasis in hypoxia induced insulin resistance.

Metformin (which activates AMPK pathway) increased the risk of lactic acidosis in patients with renal disease and hepatic disease (Ralph De Fronzo *et al.,* 2016). Hence, AMPK activates glucose uptake by a pathway distinct from that mediated by insulin, pharmacological direct activation of the AMPK pathway by NO may allow an alternative mechanism for increasing glucose uptake. Further studies can be done to find the effect of NO in the activation of AMPK would pave the way for an attractive new alternative in the treatment of diabetic patients.

The strength of this present study is the negative correlation observed between NO and IR in both prediabetes and OSA. Hypoxia could lead to decreased production of NO, as oxygen is a co-substrate (Thomas DD 2015). If association of HIF alpha 1 gene polymorphism is demonstrated in OSA and/or prediabetes, it may help to find out whether hypoxia is an underlying risk factor for diabetes.

CONCLUSION

This study has facilitated understanding of the correlation between NO and insulin resistance. Nitric oxide may have important functional role in OSA patients; Activation of AMPK by pharmacological agents like NO may be a unique challenge in managing the complexity of the disease, but holds a considerable potential to reverse insulin resistance. As NO may be the missing link in activation of the AMPK pathway in hypoxic condition, it can lead to novel therapeutic strategies for pharmacotherapy and also to understand whether NO can be utilised as an assistive tool in the early diagnosis and in prevention of high risk OSA group to develop type 2 diabetes at an early stage.

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