Short Communication

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Spatial Relationship of Metabolomics, Osa and Diabetes Mellitus

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Abstract

Metabolomics is the study of metabolites, targeted or untargeted. They can be analyzed from body fluids like urine, blood, saliva. They are of low molecular weight (<1KD). These reflect the process involved in the metabolism. The targeted one is restricted to the known metabolites. The untargeted identifies unknown metabolites, known as Metabolomes. Sleep is triphasic consisting of Sleep Latency, synchronized sleep phase (SWS) and Rapid eye moment (REM) phase.

This is essentially marshaled by neuro hormonal and metabolic changes.. Several disorders of sleep and associated hormonal imbalances can result in obesity and Diabetes Mellitus. Thus the abnormal metabolimic facsimile can reflect of this patho physiological process. The study of metabolites may pay an inexpensive way to diagnose this problem in future, fortifying or replacing Polysomnography.

Abbreviations:

SWS : Slow Wave Sleep
OSA : Obstructive sleep apnea
DM : Direct message
HCRT : Hyperthermo-Chemo Radio-Therapy
MCH : Mean cell hemoglobin

Introduction

Study of metabolomics reveals targeted or untargeted metabolites from the body fluids like saliva, blood or urine. The untargeted metabolites are known as metabolomes. This encompasses the horizon of pulmonology and sleep disorders. Besides the mandatory clinical examination of upper respiratory tract, for the Mallampatti1 grading of the oropharynx, lungs, radiological investigations including routine Chest skiagram, CT chest, MRI pharynx, Pulmonary function test, laboratory parameters for blood sugar, lipid profile, polysomnography is mandatory to establish the sleep disorders. A myriad of special investigations like Nuclear magnetic resonance spectroscopy, Mass spectrometry coupled with Gas chromatography and liquid chromatography of the body fluids can possibly replace the cumbersome polysomnography to establish the spatial relationship of the triad of metabolomics, OSA and Diabetes Mellitus (DM) [1].

The sleep is triphasic, sleep latency, Non rapid Eye movement phase or synchronised eye movement phase (SWS) and finally the Rapid eye movement phase (REM). The sleep latency lasts for twenty to thirty minutes, followed by the SWS and REM phases each lasting for one hour to ninety minutes alternatively, whole night. The whole sleep cycle of seven to nine hours is guided by neurohormonal mechanism. Obstructive Sleep Apnoea (OSA) is a moribund phenomenon occurring mostly in the REM phase, with various pathophysiological changes and obesity. Furthermore Diabetes Mellitus, a metabolic abnormality goes hand and hand with obesity and OSA. It is known that both have a two way pathologic pathway. Thus the triad of Metabolomics, OSA and Diabetes Mellitus have a spatial relation ship which is elaborated in this script.

Metabolism of an organism is the interplay of built up energy-2anabolism from the nutrients and catabolism-burning up the energy, to provide life sustaining force, involving series of complex biochemical pathways and genetic factors The main aim is to explore new biomarkers in pathophysiological state, helping diagnosis of a disease process [2]. Wang et al in a comparative study of twelve years found that the branch chained amino acids can presage the future onset of diabetes in individuals, not withstanding parameters like BMI, obesity and other risk factors, solely depending on the metabolomics from blood [3].

Karine Spiegel et al after extensive study of curtailed sleep duration found that chronic sleep loss is associated with decreased glucose tolerance, reduced leptin levels, increment in the evening cortical levels and cardiovascular effects [4].

Antonie and Lowis in their review article extrapolated the vivid relationship between the orexin or hypocretin (HCRT) system and melanin concentrating hormone (MCH) system in the hypothalamus along with the inter relationship between the grehlin- an appetite stimulating hormone in the stomach and leptin hormone, which antagonizes the grehlin [5]. They propounded that chronic sleep

deprivation result in lower leptin levels, with propensity for obesity and type 2 diabetes mellitus. This system of HCRT-MCH acts like a local circuit within hypothalamus, tagging sleep-wake cycle with metabolism .Further, there was a mention about self-reported sleep duration and BMI. Leptin –a hormone found in the adipose tissue, peripherally signaling energy to brain is influenced by sleep duration. It is basically appetite suppressant, in contrast to grehlin, another peripheral hormone in the stomach, which is stimulant. Most prominent among the hormonal systems that interact with leptin as well as with sleep regulation are the hypothalamo-pituitary-adrenal axis and glucose regulation by insulin.

Experimental sleep deprivation has been found to alter immune response and increase proinflammatory markers such as IL-6, TNF-α, and CRP [2].

Chronic Sleep duration of less than five hours or prolonged sleep for more than nine hours seems to induce type 2 diabetes mellitus in males in an experimental study. In the normal physiology of sleep growth hormone and cortisol have important role in the SWS phase and REM phase respectively. There tends to be hyperglycaemia and insulin resistance in the SWS phase. There is also upsurge in the leptin and grehlin, peripheral hormone levels, the former originating from the adipose tissue and the later from the stomach. The interplay5 between growth hormone, insulin resistance, leptin an anorexogenic and the grehelin, an appetite stimulating hormone result in hyperglycaemia in the SWS phase. However, it appears that the leptin seems to control the appetite along with the excitary neuropeptide hormones Orexin A and B from the anterior part of the thalamus. The orexin neurons are spread over paraventricular nucleus of thalamus, the arcuate nucleus, the locus coerueus and tuberomammilary nucleus, which is involved in wakefulness. However this does not spread to cerebellum.

Obstructive sleep apnoea is a significant pathological aspect of the abnormal sleep characterised by snoring, obesity, daytime sleepiness and more often than not accompanied by diabetes mellitus. The biochemical changes occurring in this moribund condition are:

1. Increased low density lipids
2. Decreased high density cholesterol
3. Increased triglycerides
4. Dyslipidaemia
5. Increased several fatty acid derivatives, which are not normally found 6.finally increased total cholesterol.

Sleep loss or deprivation may induce inflammatory cytokinins and enhance the level of C-reactive protein in the serum [6,7].

Xu et.al found in their study in OSA comparing with normal individuals that there occurred an increase of the following: [8]

- 2,4-dihydroxybutyric acid, 2-hydroxy-3-methylbutyric acid, 3,4-dihydrxoybutyric acid, 6-aminocaproic acid, Pentanoic acid.
- Furthermore, it was also found decrement of glyceraldehyde and bile acid glycochenodeoxycholate-3-sulfate (GCDCA-3-sulfate).
- There seems to be pan metabolic abnormality engulfing the amino acid and carbohydrate metabolism as well. There was significant reduction, in methylcysteine and serine.

Over and above phospholipids biosynthesis, carbohydrate metabolism, TCA, glutamate metabolism, nucleic acid metabolism,indoles with its'derrivatives,spermine and tyrosine metabolism were also deranged significantly. The complex chain reactions lead to hypoxia of the cell, which in turn leads to several irreversible changes as shown in the diagram, culling ultimately to type 2 Diabetes Mellitus. This is suitably depicted in the following flow chart.

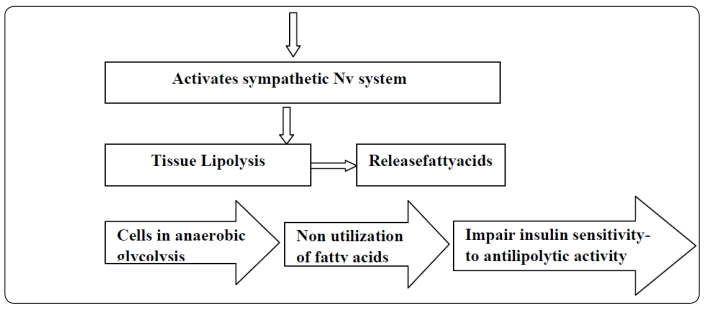

Figure 1: Intermittent hypoxia

There are myriad of sleep disorders, some of which are Attributable to the modern life style of compromised sleep duration, working in shifts and pre existent Diabetes Mellitus and or OSA.

Sharma and kavur2 in their review article adumbrated the complex relationship between the triad of metabolism, sleep and Diabetes mellitus. The triad of shift workers disorders of sleep, lack of sleep and OSA have common pathway of leading to type 2 Diabetes Mellitus. The shift workers disorders of sleep lead to decreased glucose tolerance as a play of hormonal changes specially leptin and grehlin, the latter taking the upper hand. Similarly the other side of the coin is the lack of sleep and habitual insomnia. This tends to increased food intake, fatigue, hormonal changes –specially decreased leptin and increased grehlin action. Finally, this also tends to increased insulin resistance, hyperglycaemia and diabetes mellitus. The following figure shows the intricate relationship of the sleep and metabolism.

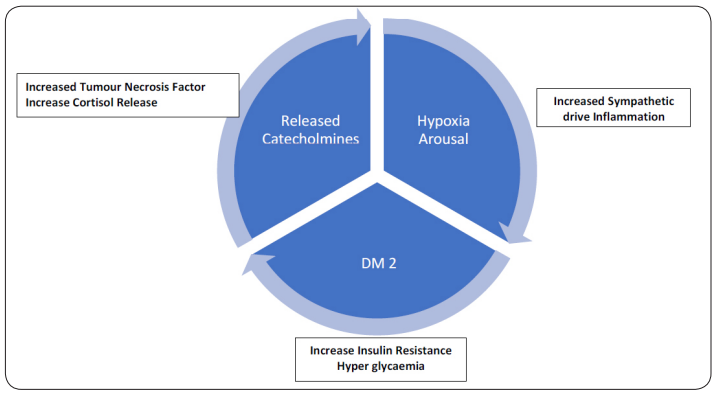

Figure 2: Shift Workers Disorder/OSA/Sleep Loss & DM

The neuro hormonal factors, metabolites and the sleep disorders can conveniently construed in the form of a triangle as shown in the diagram.

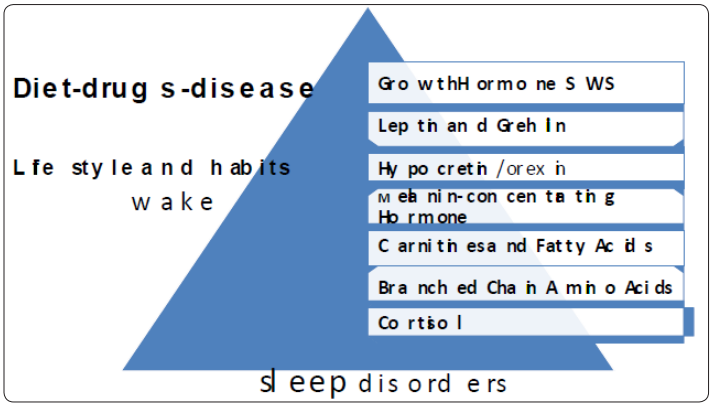

Figure 3: Hypothalamus and other Nervous System & Metabolites

To summarise, the study of metabolomics is a concept of diagnosing the sleep disorders from the metabolomes in a simpler way by passing the costly polysomnography and establishing the spatial relationship with diabetes mellitus type 2 However, this also involves the advent of the Mass spectrometry coupled with Gas chromatography and Liquid chromatography. It is a conjecture that how many centres are equipped with the equipment and state of the art. Research has only a beginning and will not be only a parable.

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