ACTA SCIENTIFIC MEDICAL SCIENCES

Volume 3 Issue 3 March 2019

Review Article

Relationship between Insulin Resistance and Metabolic Syndrome Clusters: Current Knowledge

Christopher Edet Ekpenyong*

Department of Physiology, Faculty of Basic Medical Sciences, University of Uyo, Uyo, Nigeria

***Corresponding Author:** Christopher Edet Ekpenyong, Department of Physiology, Faculty of Basic Medical Sciences, University of Uyo, Uyo, Nigeria.

Received: January 21, 2019; **Published:** February 15, 2019

Abstract

Insulin resistance has emerged as the key metabolic defect that orchestrates a cluster of metabolic disorders such as hyperglycemia, hypertension, dyslipidemia, hyperuricemia and obesity. However, despite the extensive studies on the relationship between insulin resistance and metabolic syndrome clusters, there is a lack of literature review on current knowledge about the mechanistic links between insulin resistance and clusters of these metabolic aberrations.

The aim of this review was to synthesize, analyze and provide current information based on recently published articles that highlighted the relationship between insulin resistance and metabolic syndrome clusters.

Literature search was performed using Google scholar, PubMed, Medline and Embase search engines to identify English language articles published up to November 2018 that explored the relationship between insulin resistance and dysmetabolic syndrome clusters.

Empirical data provide insight into the intricate mechanisms of insulin resistance induced metabolic disorders, including insulin resistance-induced depletion of nitric oxide, nicotinamide adenine dinucleotide phosphate hydrogen oxidase leading to increase reactive oxygen species, increased renal tubular sodium re-absorption, impaired renal uric acid clearance, alteration in trans-membrane ion transport, activation of sympathetic nervous system, upregulation of angiotensin II receptor, and impairment of adipose tissue lipoprotein lipase activity etc.

This review confirms the co-existence of insulin resistance and metabolic syndrome clusters as a cost-effect relationship

Keywords: Hyperinsulinemia; Hypertension; Hyperglycemia; Dyslipidemia; Overweight; Obesity; Hyperuricemia

Introduction

Central in the etiology of many metabolic disorders is insulin resistance (IR), a state of cellular non-responsiveness to insulin stimulation. Insulin actions promote energy utilization and storage in addition to the operation of other signaling pathways. Under the influence of an IR state, the body "starves in the midst of plenty." With a continuous production of insulin with little or no utilization, the body is saturated with a condition of insulin and glucose excess (hyperinsulinemia and hyperglycemia, respectively) in the presence of excess fatty acids [1]. The interaction between the hyperinsulinemia, IR, and compensatory hyperinsulinemia has been described in the literature [2]. It is known that glucose is generated from dietary carbohydrates following the digestive action of different gastrointestinal enzymes. As a follow-up, the glucose molecules are rapidly absorbed and plasma glucose is elevated. The resulting postprandial hyperglycemia is associated with the increase in glucose-dependent insulin-like polypeptide and glucagon-like polypeptide-1 secreted from the gut, which stimulates pancreatic insulin secretion resulting in an acute plasma insulin tide [3]. However the determinants for the degree of the acute postprandial hyperglycemic and hyperinsulinemic response to dietary carbohydrate are the glycemic load [4] and glycemic index of the carbohydrate ingested. If a mixed meal consisting of protein and fats along with carbohydrate is consumed, there will be a lowering in the total glycemic and subsequent insulinemic responses [5]. Interestingly, when the skeletal muscle (principally), liver, adipose tissue, and endothelial tissue develop resistance to insulin-mediated glucose uptake, a condition described as IR develops [6]. IR is an important worldwide health issue, and many propositions have been made regarding the molecular basis of peripheral IR [7]. Even when pe-

ripheral tissues are resistant to insulin-mediated glucose-lowering effects in plasma, the pancreas still secretes additional insulin, which can prevent the long-term glucose concentration from rising in a pathological pattern. Compensatory hyperinsulinemia, therefore, is the maintenance of normal blood glucose via an elevated plasma insulin concentration. The onset of impaired glucose tolerance/type 2 diabetes mellitus (T2DM) indicates that stage in which the pancreas fails to maintain compensatory hyperinsulinemia, which is the fundamental metabolic disturbance underlying the metabolic syndrome (MetS) [7].

The hyperinsulinemic state in association with the IR state orchestrates a symphony of metabolic disorders, namely elevated triglycerides (TGs) [8], low HDL [9], high blood pressure, coronary arterial diseases, T2DM and obesity [10].

Methods

Literature search was conducted using Google Scholar, PubMed, MEDLINE and Embase search engines to identify English language articles published up to November 2018 that explored the relationship between IR and metabolic syndrome clusters. A pre-specified search string including search terms on the relationship between IR and hyperglycemia, hypertension, obesity, dyslipidemia and hyperuricemia was used for PubMed, MEDLINE, Embase and Google Scholar.

For each article selected, the mechanistic links between IR and metabolic disorders were considered. These included the depletion of nitric oxide (NO), and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase and leading to increase reactive oxygen species (ROS). IR-induced renal tubular sodium (Na+) re-absorption, impaired uric acid (UA) clearance, alteration in transmembrane ion transport, activation of sympathetic nervous system, upregulation of angiotensin II receptor and impairment of adipose tissue lipoprotein lipase activity were also considered.

In all, 170 articles were selected and after applying the exclusion criteria such as articles with obvious methodology flaws, unadjusted confounders and duplicated data. Eighty-two (82) articles were finally included in the review. Each article was evaluated for the type of study and the study design.

Insulin resistance and Dyslipidemia

Many studies suggest that IR could be implicated in the etiology of dyslipidemia [11]. In fact, listed among the characteristic lipoprotein abnormalities associated with IR are high very-low-density lipoprotein (VLDL) levels, low high-density lipoprotein (HDL)-cholesterol and apolipoprotein A-1 (apoA-1) levels, and, most commonly, hypertriglyceridemia [11]. In fact, further investigation has shown that a ratio of high TG to HDL-cholesterol is the single most distinctive feature of the IR syndrome, even more highly predictive of IR than the presence of abdominal obesity [12].

Evidently, insulin has profound effects on HDL metabolism, and low HDL-cholesterol and apoA-1levels and a high ratio of total cholesterol to HDL-cholesterol are strongly related to IR, especially in insulin-dependent DM (IDDM) [13]. Insulin has a profound influence on VLDL metabolism but less influence on LDL metabolism [14]. A reduced effect of insulin in subjects with IR may result in excessive adipose tissue lipoprotein lipase (LPL) and elevated hepatic TG lipase activity; in turn, this diminished LPL activity in IR subjects is postulated to reduce VLDL catabolism and further mitigate hypertriglyceridemia [11,12]. Additionally, the reduction in LPL activity in IR states may also affect hydrolysis of chylomicron TGs; particularly if excessive hepatic VLDL production saturates all available LPL binding sites [11,12]. This invariably leads to excessive mobilization of TGs from the TG rich chylomicrons and VLDL particles in lieu of HDL particles derived from cholesterol esters, thus resulting in low HDL-cholesterol levels [11]. Aside from the reduction in LPL activity, reduced HDL levels in the IR state are associated with reduced lecithin cholesterol acyltransferase and cholesterol ester transfer protein activity [13].

In summary, in the review by Rashid., *et al*. [12], it was proposed that the TG-rich HDL particles formed are also cleared more rapidly from the circulation than non-TG-rich HDL owing to one or more of the following three mechanisms: 1) TG-rich, cholesterol-depleted HDL particles have been shown to be thermodynamically instable, having their apoA-I in a more loosely bound form; 2) TG-rich HDLs are more readily lipolyzed by hepatic lipase, thereby reducing HDL size, and resulting in free apoA-I or lipid-poor pre-β1 particles (containing apoA-I together with a small amount of lipid) being shed from the particles 3) the HDL remnant particles that have been reduced in size may themselves be more readily cleared from the circulation. The above processes may then enhance the HDL apoA-I fractional catabolic rate. The end result is a lowering of HDL-C and apoA-I levels in plasma.

Insulin resistance and Hypertension

The relationship existing between IR and hypertension has been the subject of many empirical studies conducted in both human and animal models. However, it is disputable whether high

blood pressure or hypertension is the product of the IR state or vice versa. Evidently, IR and hypertension are both components of the MetS and often coexist in individuals [15]. In comparison, approximately 50% of hypertensive individuals also present with hyperinsulinemia or glucose intolerance, whereas approximately 80% of T2DM patients are also hypertensive [16]. In addition to its effects on body metabolism and the energy cycle, insulin contributes to blood pressure regulation by stimulating the production of nitric oxide (NO) in endothelium, which induces vasorelaxation [17] and regulates sodium homeostasis by enhancing sodium reabsorption in the kidney [18]. It has been shown that insulin can regulate epithelial sodium channels and the Na+/H+ exchanger, therefore increasing renal tubular sodium re-absorption [19].

Because IR has been shown to enhance the blood pressure response to sodium intake, reduction in sodium intake may be especially beneficial in reducing blood pressure in patients who are prone to IR and the MetS [15].

In many studies, an association between hyperinsulinemia and IR has been found in hypertensive patients [20]. Patients with untreated essential hypertension often present with classical features of IR and a compensatory hyperinsulinemia. The coexistence of IR and hypertension can be viewed as a cause-effect relationship (in which IR serves as a cause of hypertension or vice versa) or as a no causal association [21]. IR is believed to increase blood pressure via several mechanisms: increased renal sodium reabsorption, alteration of transmembrane ion transport, hypertrophy of resistance vessels, and activation of the sympathetic nervous system and up-regulation of angiotensin II receptors by a post-translational mechanism [21,22].

Conversely, hypertension can cause IR by altering the delivery of insulin and glucose to skeletal muscle cells, resulting in impaired glucose uptake. The common pathogenetic mechanism for both IR and hypertension is believed to be the activation of the sympathetic nervous system [21].

In an acute phase, insulin has been shown to stimulate sympathetic nervous system activity and transmembrane electrolyte transport, to promote sodium retention, and to cause vascular wall changes, including increased cholesterol biosynthesis and smooth muscle proliferation. In a chronic condition, the continuous exposure to elevated plasma insulin levels may play a pathogenetic role in the development of high blood pressure and also predispose patients with hypertension toward atherosclerosis [20]. In fact, chronically, hyperinsulinemia may promote cardiovascular muscle cell proliferation and atherogenesis, whereas IR may be associated with certain transmembrane cation transporters, leading to an increase in cytosolic Ca^{2+} [22]. The roles of both IR and hyperinsulinemia in hypertension are believed to involve a slow pressor mechanism [22].

Insulin resistance, Obesity, and Hyperglycemia

The obese state has been shown to be associated with increased risk of IR and T2DM in various experimental studies in both humans and animals [23]. In fact, obesity is regarded as the most common cause of IR [24]. Consequently, many propositions have been put forth to validate the links between obesity, T2DM, and IR as summarized in this section.

The mechanism underlying the increased adipose tissue mass-induced reduction in insulin sensitivity in adipose tissue and in other tissues including liver and skeletal muscle has become better understood. In obese individuals, adipose tissue has-been shown to release a number of factors (non-esterified fatty acids, glycerol, hormones and neurotransmitters such as cortisol and norepinephrine, and inflammatory cytokines) in increased amounts that are involved in the development of IR [25].

In the review by Quatanani and Lazar [25], it was further explained how these factors link obesity to IR,1) The obesity-associated increase in fatty acids can trigger IR through intracellular metabolites that activate protein kinase C, leading to the activation of serine/threonine kinases that inhibit insulin signaling [26]. Furthermore, fatty acids are said to cause a defect in glucose transport by inhibiting insulin-stimulated tyrosine phosphorylation of IRS-1 and IRS-1-associated phosphatidyl activity. It could be said that the increase in fat delivery to muscle and liver as a consequence of either excess energy consumption resulting from a defective adipocyte fat metabolism or an acquired defect in mitochondrial fatty acids oxidation is among the different metabolic abnormalities that may increase intramyocellular/intrahepatic fatty acids metabolites [27]. 2) An obesity-associated increase in adipose mass could lead to pathological changes in adiposity hormones (adipokines) that regulate insulin sensitivity [25]. 3) An obesity-associated increase in the accumulation of inflammatory factors such as adipose tissue macrophages, which increase the adipose tissue production of inflammatory cytokines, inhibits insulin signaling [28]. 4) Endocrine and inflammatory mediators converging on serine/threonine kinases also inhibit insulin signaling. 5) Activation of NFκB heightens inflammatory responses that exacerbate IR [30]. 6) Suppressors of cytokine signaling family proteins, induced by adipokines, induce IR either by interfering with IRS-1 and IRS-2 tyrosine phosphorylation or by targeting IRS-1 and IRS-2 for proteasomal degradation [31]. 7) Free fatty acids also trigger IR by direct activation of Toll-like receptor 4 and the innate immune response [32]. 8) An obesity-related alteration in the central response to hormonal and nutrient signals alters peripheral insulin sensitivity. It is opined that

decreasing hypothalamic insulin receptors causes hyperphagia and IR in rats [25].

Furthermore, increased accumulation of TGs and other lipids characterizing obesity leads to ectopic fat storage [25]. This in turn results in an increase in the circulation of fatty acid metabolite, diacylglycerol, and long-chain fatty acyl-coenzyme A, whose activities inhibit insulin signaling through the allosteric activation of PKCs (PKC-β, -δ, and -θ) in liver and muscle [27]. Excess accumulation of lipids could also trigger an increase in reactive oxygen species (ROS) generated by mitochondrial oxidation [23]. An excess in ROS leads to activation of several serine/threonine kinases (such as JNK, IKK, (IκB kinase) and p38 MAPK) that inhibit insulin signaling either directly through IRS-1 or IRS-2 serine phosphorylation or indirectly through a series of transcriptional events mediated by NFκB [33]. Specifically, ROS are shown to stimulate pro-inflammatory signaling by the activation of IKKβ, which then phosphorylates IRS-1 at the serine residue [23]. Furthermore, obesity leads to the activation of cellular endoplasmic reticulum stress responses that suppress insulin signaling through the activation of JNK or through a potential increase in ROS production [34]. Endoplasmic reticulum stress is another mechanism that could also contribute to IR via serine kinase activation. However, JNK activation, as a consequence of endoplasmic reticulum stress, increases serine phosphorylation of IRS proteins [23]. Hence, it could be substantially inferred that inflammation could also link IR with obesity and T2DM [35].

Insulin resistance and Hyperuricemia

Hyperuricemia has been identified as an independent and significant risk factor for IR in several epidemiological studies [36-38]. In most of these studies, increasing serum uric acid (SUA) level independently increased the risk for IR and vice versa. For instance, in a 15-year follow-up study of 5,012 young adults in 4 US cities, the authors reported that higher SUA level (hyperuricemia) conferred higher risk for IR, diabetes and pre-diabetes on the participants [39].

Vuorinen-Markkola and Yki-Jarinen [36] in a simple linear regression analysis found that SUA concentration was inversely correlated with insulin sensitivity, independent of BMI, age and plasma glucose concentration. Multiple linear regression analysis further confirmed the independent association of SUA level with insulin sensitivity and triglyceride. Conen., *et al*. [37] found the same pattern, direct association of hyperuricemia with IR in Seychelles.

In some other studies the inverse association was influenced by demographic variables (age and gender), or the presence of one or more components of metabolic syndrome clusters (obesity, diabetes mellitus, hypertension and hyper-triglyceridemia) [40]. Accordingly, Yoo., *et al*. [38] found that SUA was independently correlated with IR, hypertension and risk factors for metabolic syndrome.

One study among hospitalized older men and women demonstrated positive and significant association between hyperuricemia and age, adiposity indices, blood pressure indices (systolic and diastolic), HDL and TG [41] in both male and female participants. Also, de-Miranda and Colleagues [42] reported similar pattern, a direct but significant relationship between SUA level and IR in children and adolescents with obesity.

In a multivariable adjusted for almost all potential covariates except potential adiposity mediators, Mazidi and Colleague [43] demonstrated a positive and significant relationship between SUA and glucose/insulin homeostasis parameters (C-reactive protein, insulin, HOMA-IR, HOMA-B, 2-h blood glucose and triglyceride). Interestingly, these parameters were significantly and positively influenced either partially or fully by the potential adiposity mediators.

Furthermore, in 2011, Abreu., *et al*. [44] studied 1370 (852 men and 518 women) Portuguese adults and found higher prevalence of IR among hyperuricemic participants with men having higher prevalence of IR than women. In a community based prospective study among people aged > 40 years in Taiwan, Chen., *et al*. [45] reported similar association between hyperuricemia and IR only in older women but not in men. However, in men metabolic syndrome was significantly associated with IR.

Although a number of studies documented a significant positive correlation between hyperuricemia and IR, controversies exist about which one precedes the other. However, it is now postulated that hyperuricemia probably precedes IR [39], while IR partially mediates the effect of UA in the pathogenesis of metabolic syndrome clusters [46].

In a recent research, Han and Colleagues [46] demonstrated a unidirectional relationship from uric acid to hepatic and peripheral IR among hypertensive subjects in a study to elucidate the temporal sequence of hyperuricemia and IR in the pathogenesis of hypertension.

In some other studies [47] lowering SUA levels decreased markers of IR including fasting insulin levels, further supporting the sequence from hyperuricemia to IR. UA is postulated to induce peripheral IR through 2 major mechanisms (1) depletion of nitric oxide (NO) bio-availability and supply [48] and (2) activation of NADPH oxidase and leading to increase ROS, oxidized lipids and inflammatory markers in adipocytes. Robles-Cervantes and col-

leagues [49] demonstrated positive relationship of SUA level with the total phase of insulin secretion even in states prior to hyperuricemia in patients with T2DM, suggesting the role of UA in beta cell function.

Some other authors argued that IR precedes hyperuricemia in view of the effect of IR on renal urate clearance and SUA levels. IR inhibits renal UA excretion, and leading to hyperuricemia by increasing renal tubular sodium re-absorption. Adiposity mediated IR-induced hyperuricemia has also been implicated. In which direction the association exist more is controversial, however factors analysis implicates the effect of several other covariates in the association. Nevertheless, there is a significant correlation between SUA level and IR.

Conclusion

Literature evidence supports a cost-effect relationship between IR and Mets clusters.

Bibliography

1. Ye J. "Role of insulin in the pathogenesis of free fatty acid-induced insulin resistance in skeletal muscle". *Endocrine, Metabolic and Immune Disorders - Drug Targets* 7 (2007): 65-74.

2. Reaven GM. "Syndrome X: 6 years later". *Journal of Internal Medicine* 236 (1994): 13-26.

3. Cordian L., *et al*. "Origins and evolution of the Western diet: Health implications for the 21st century". *The American Journal of Clinical Nutrition* 81 (2005): 341-354.

4. Ludwig DS. "The glycemic index: physiological mechanisms relating obesity, diabetes and cardiovascular disease". *JAMA* 287 (2002): 2414-2423.

5. Wolever TM and Jenkins DJ. "The use of the glycemic index in predicting the blood glucose response to mixed meals". *The American Journal of Clinical Nutrition* 43 (1986): 167-172.

6. Beck-Nielsen H. "Insulin resistance: organ manifestation and cellular mechanism". *Ugeskr Laeger* 164 (2002): 2130-2135.

7. Reaven GM. "Insulin resistance and its consequences". In: Le Roith D, Taylor SI, Olefasky JM, eds. Diabetes mellitus: a fundamental and clinical text. 3rd ed. Philadelphia: Lippincott, Williams and Wilkins (2004): 899-915.

8. Godland IF., *et al*. "Influence of insulin resistance, secretion and clearance on serum cholesterol, triglycerides, lipoprotein cholesterol and blood pressure in healthy men". *Arteriosclerosis, Thrombosis, and Vascular Biology* 12 (1992): 1030-1033.

9. Karhapaa P., *et al*. "Isolated low HDL cholesterol: An insulin-resistant state". *Diabetes* 43 (1994): 411-417.

10. Goldstein BJ. "Insulin resistance as the core defect in type 2 diabetes mellitus". *The American Journal of Cardiology* 90 (2002): 3-10.

11. Reaven G. "Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease". *Circulation* 106 (2002): 28-38.

12. Abate N., *et al*. "Abnormal cholesterol distribution among lipoprotein fractions in normolipidemic patients with mild NIDDM". *Atherosclerosis* 118 (1995): 111-122.

13. Laakso M., *et al*. "Insulin resistance is associated with lipid and lipoprotein abnormalities in subjects with varying degrees of glucose tolerance". *Arteriosclerosis* 10 (1990): 223-231.

14. Zhou MS., *et al*. "Link between insulin resistance and hypertension: what is the evidence from evolutionary biology?" *Diabetology and Metabolic Syndrome* 6 (2014): 12.

15. Lastra G., *et al*. "Salt, aldosterone, and insulin resistance: impact on the cardiovascular system". *Nature Reviews Cardiology* 7 (2010): 577-584.

16. Scherrer U., *et al*. "Nitric oxide release accounts for insulin's vascular effects in humans". *Journal of Clinical Investigation* 94 (1994): 2511-2515.

17. Horita S., *et al*. "Insulin resistance, obesity, hypertension, and renal sodium transport". *International Journal of Hypertension* (2011): 391-762.

18. Pavlov TS., *et al*. "Regulation of ENaC in mice lacking renal insulin receptors in the collecting duct". *FASEB Journal* 27 (2013): 2723-2732.

19. Berne C. "Insulin resistance in hypertension; a relationship with consequences". *Journal of Internal Medicine* 735 (1991): 65-73.

20. Salvetti A., *et al*. "The interrelationship between insulin resistance and hypertension". *Drugs* 46 (1993): 149-159.

21. De Fronzo RA., *et al*. "Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease". *Diabetes Care* 14 (1991): 173-194.

22. Rao G. "Insulin resistance syndrome". *American Family Physician* 63 (2001): 1159-1163.

23. Reaven G. "Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease". *Circulation* 106 (2002): 28-38.

24. Quatanani M., *et al*. "Mechanisms of obesity associated insulin resistance: many choices on the menu". *GENES and Development* 21 (2007): 1443-1445.

25. Randle PJ., *et al*. "The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus". *Lancet* 1 (1963): 785-789.

26. Boden G. "Role of fatty acids in the pathogenesis of insulin resistance and NIDDM". *Diabetes* 46 (1997): 3-10.

27. Lumeng CN., *et al*. "Obesity induces a phenotypic switch in adipose tissue macrophage polarization". *Journal of Clinical Investigation* 117 (2007): 175-184.

28. Hirosumi J., *et al*. "A central role for JNK in obesity and insulin resistance". *Nature* 420 (2002): 333-336.

29. Yuan M., *et al*. "Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikk". *Science* 293 (2001): 1673-1677.

30. Rui L., *et al*. "SOCS-1 and SOCS-3 block insulin signaling by ubiquitin-mediated degradation of IRS1 and IRS2". *Journal of Biological Chemistry* 277 (2002): 42394-42398.

31. Shi H., *et al*. "TLR4 links innate immunity and fatty acid- induced insulin resistance". *Journal of Clinical Investigation* 116 (2006): 3015-3025.

32. Kyriakis JM and Avruch J. "Sounding the alarm: Protein kinase cascades activated by stress and inflammation". *Journal of Biological Chemistry* 271 (1996): 24313-24316.

33. Ozcan U., *et al*. "Endoplasmic reticulum stress link obesity, insulin action and type 2 diabetes". *Science* 306 (2004): 457-461.

34. Savage DS., *et al*. "Mechanism of insulin resistance in humans and possible link with inflammation". *Hypertension* 45 (2005): 828-833.

35. Vuorinen Markkola H and Yki-Jarvinen H. "Hyperuricemia and insulin resistance". *The Journal of Clinical Endocrinology and Metabolism* 78 (1994): 25-29.

36. Conen D., *et al*. "Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country". *BMC Public Health* (2004).

37. Yoo TW., *et al*. "Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome". *The Clinical Journal* 69 (2005): 928-933.

38. Krishnan E., *et al*. "Hyperuricemia in young adults and risk of insulin resistance, pre-diabetes and diabetes: A 15year follow-up study". *American Journal of Epidemiology* 176 (2012): 108-116.

39. Robles-Cervantes JA., *et al*. "Relationship between serum concentration of uric acid and insulin secretion among adults with type 2 diabetes mellitus". *International Journal of Endocrinology* (2011).

40. Rahman TTH. "Prevalence of hyperuricemia among hospitalized elderly patients and its association with metabolic syndrome". *Advances in Aging Research* 3 (2014): 329-337.

41. De-Miranda JA., *et al*. "The role of uric acid in the insulin resistance in children and adolescent with obesity". *Revista Paulista de Pediatria* 33 (2015): 431-436.

42. Mazidi M., *et al*. "The link between insulin resistance parameters and serum uric acid is mediated by adiposity". *Atherosclerosis* 270 (2018): 180-186.

43. Abreu E., *et al*. "Association between Hyperuricemia and insulin resistance". *Acta Médica Portuguesa* 24 (2011) 565-574.

44. Chen L-K., *et al*. "Uric acid: A surrogate of insulin resistance in older women". *The European Menopause Journal* 59 (2008): 55-61.

45. Han T., *et al*. "Temporal relationship between hyperuricemia and insulin resistance and its impact on future risk of hyperuricemia". *Hypertension* 70 (2017): 703-711.

46. Brymora A., *et al*. "Low-fructose diet lowers blood pressure and inflammation in patients with chronic kidney disease". *Nephrology Dialysis Transplantation* 27 (2012): 608-612.

47. Khosla UM., *et al*. "Hyperuricemia indices endothelial dysfunction". *Kidney International* 67 (2005): 1739-1742.

48. Johnson RJ., *et al*. "Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease?" *Hypertension* 41 (2003): 1183-1990.

49. Kanellis J and Kang DH. "Uric acid as a mediator of endothelial dysfunction, inflammation and vascular disease". *Seminars in Neurology* 25 (2005): 39-42.

Volume 3 Issue 3 March 2019