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Review Article

A Review of Contemporary Markers of Insulin Resistance

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Abstract: Backgrounnd: The era of non-communicable diseases has been here with us for a while. Diabetes mellitus, pre-diabetes, insulin resistance, metabolic syndrome and associated complications; have been the centre of interest for many researchers lately. Insulin resistance (IR) has taken a forefront position in this regard. Aim: Insulin resistance has been implicated in the pathogenesis of many metabolic disorders. It heralds the onset of many of these diseases many years before the clinical signs and symptoms. Method: A thorough literature search was done using internet academic search engines and indexation such Google scholar, hinari, Ebsco, Scorpus, etc. Results: Insulin resistance (IR), an independent risk factor for the development of Type 2 diabetes and metabolic syndrome is assessed by several biomarkers. From the historical perspective till date, the authors assess the implication, connection and relevance from various studies to contemporary scientific breakthroughs in this regard for diagnosis and clinical application of markers of insulin resistance in patient management. Conclusion: It is hoped that with the advancement in medical research, more markers of insulin resistance will be discovered that will help in patient managements.

Keywords: Insulin Resistance, Markers, Diabetes, Metabolic Syndrome, Diseases

1. Introduction

In the last few years, metabolic medicine has been the focus of many research works globally. The era of non-communicable diseases has been here with us for a while. Diabetes mellitus, pre-diabetes, insulin resistance, metabolic syndrome and associated complications; have been the centre of interest for many researchers lately. Insulin resistance (IR) has taken a forefront position in this regard [1].

Insulin resistance (IR), an independent risk factor for the development of Type 2 diabetes and metabolic syndrome is defined as a pathological condition characterized by failure of the body cells to respond normally to insulin [1-3] from blood to muscles and body tissues [1-3]. IR is a known predictor of cardiovascular risk, and is associated with obesity, impaired glucose tolerance, type 2, diabetes and other metabolic changes [4, 5]. IR is the primary metabolic disorder associated with obesity and appears to be the primary mediator of metabolic syndrome [6].

2. Historical Concept

The concept of IR as being the underlying cause of Type 2 diabetes was advocated by Prof. Wilhem Falt and published in 1931; and confirmed in 1936 by Sir Harold Hinsworth of the University College Hospital, London [7, 8].

Insulin resistance underpins the development of type 2 diabetes mellitus (DM), and is reportedly said to be responsible for the increased vascular risk associated for type 2 DM [9].

3. Insulin Resistance and Diseases Correlation

Proofs have been noted severally that reduction in IR has been shown to improve glucose controls in diabetic patients [10]. IR has been seen as the hallmark of obesity, type 2 diabetes mellitus, and cardiovascular disease and also leads to metabolic syndrome [11]. It has been found to precede the

foundation of many cardiovascular diseases. It contributes significantly to the aetio-pathogenesis of impaired glucose tolerance, type 2 DM, and obesity [12]. It also plays a role in the pathogenesis of dyslipidemia [13-15].

IR is related to waist circumference, hyperglycemia, and dyslipidemia with a distortion of lipid profile so there is reduced high density lipoprotein cholesterol (HDL-C), and small dense low density lipoprotein (sd LDL) particles, alongside with hyper-coagulable state and also inflammatory markers [16-19]. Some researchers conclude the IR is an accelerator of cardiovascular diseases, metabolic syndrome and all the above listed [20]. It is also known that IR can be present in the absence of obesity or diabetes [21, 22]. IR has been known to precede the development of diabetes mellitus about 10 – 20 years before diabetes mellitus symptoms appears [23].

4. Aetiology

The etiology of IR ranges from congenital to acquired factors. Both genetic and environmental factors play significant roles [24]. Fetal malnutrition /under nutrition [25], Insulin receptor defect [26] to physiological conditions such as pregnancy [26], high fat diet [27], sedentary, lifestyle have all been implicated. Hormonal disorders, such as phaechromocytoma [28], steroid overdose have been implicated by some researchers [29]. In recent times, raised blood pressure and obesity and polycystic ovarian syndrome (PCOS) have been included [30-32]. It is also associated with fatty liver, acanthosis nigricans [33, 34].

Insulin resistance has no specific signs and symptoms. It may be part of metabolic syndrome. It precedes the development of type 2DM. The cause of the IR include both genetic and environmental/lifestyle factors [35].

5. Insulin Action

Insulin is a polypeptide dimer hormone produced by the beta cells of the pancreas. It is an anabolic hormone that enhances the absorption of glucose from plasma to body tissues and is made up of both alpha and beta chains. It is stimulated and released into circulation after a carbohydrate meal. Insulin resistance occurs when the tissues are sensitive to the available glucose and so they (glucose) cannot enter the body tissue. They lead to hyperglycemia which if chronic, can lead to other forms of damage to the tissue. As this continues, hyperglycemia further stimulates insulin release from the pancreas leading to hyperinsulinemia and the cycle continues [36].

6. Pathogenesis

Molecular mechanisms that explain IR are completely unclear. However, there is an inter-play between multiple genetic and environmental factors. It is a complex network of interaction. One theory concludes that hyperlipidemia in plasma (majorly hypertriglycedemia) leads to accumulation of triglycerides in the muscle which activates protein C kinase, thereby reducing the glucose uptake at any level of insulin. High lipid influx stimulates this mechanism very fast [37]. Again, another theory posits that diets rich in unsaturated fat have inverse relationship with IR. It is proven that increasing the level of PUFA concentration causes an increased number of insulin receptor which subsequent reduction in IR [38]. Stress is yet another factor which enhances IR by increased cortisol levels. Cortisol which is a counter regulatory hormone is anti-insulin and leads to increased plasma glucose leading to IR [39]. Some researchers have also added that excess fatty acid leads to modification of down-stream signaling which leads to IR.

HISTORICAL PRESENTATION OF INSULIN RESISTANCE

As far back as 1979, Turner RC *et al* came up with the finding that insulin and IR were associated with DM. They also established that the degree of basal hyperglycemia in diabetes was a reflection of the degree of insulin resistance. Among the patients they assessed, IR was a found to be a stronger factor in newly diagnosed patients than beta cell deficit in both normal weight or obese people [40]. Similarly, Defronzo went ahead to publish an article on glucose clamp technique as a method of quantifying insulin secretion or insulin resistance. They measured the tissue sensitivity to exogenous insulin. This hyperinsulinemic euglycemic glucose clamp is regarded as the gold standard for quantifying insulin sensitivity [41].

Few years later (1981), Greenfield MS *et al* assessed about 30 subjects and insulin resistance was quantified in them with various degrees of glucose tolerance. They used suppression tests alongside with euglycemic clamp. Using these two methods, they concluded that insulin resistance was directly proportional to the degree of glucose tolerance. This study further emphasized the importance of IR in the pathogenesis of hyperglycemia in Type 2 DM [42].

The concept of homeostatic model assessment (HOMA) was birthed by Matthew DR in 1985. They suggested a model of intervention between glucose and beta cell function used to predict fasting steady state and insulin concentration for a wide range of possible combinations. Both HOMA-IR and HOMA % B have found their relevance into clinical practice and have revolutionized the concept of insulin resistance assessment in patients. This is usually expressed as an equation for estimating insulin resistance and beta cell function (HOMA-IR, and HOMA % β respectively) from fasting insulin and fasting glucose samples. It has a given a big boost to assessment of IR as it is used to patients' management. This assesses both insulin insensitivity predicts fasting steady state glucose and insulin levels. It is minimally invasive [43].

$$HOMA\ IR = \frac{Glucose\ x\ Insulin}{22.5}$$ (Glucose values in mmol/L) [44]

$$\text{HOMA} - \text{B\%} = \frac{-20\ \text{X Insulin (mu/L)}}{\text{Glucose} - 3.5} \text{(glucose in mmol/L)}$$

In 2001, Matthew KJ et al came up with the quantitative insulin check index (QUICK 1) which was a logarithmically

transformed deviation of the fasting plasma glucose and insulin levels. QUICK1 is a mathematical transformation of fasting plasma glucose and insulin. It is a consistent and precise index of insulin sensitivity. It is minimally invasive and given by the formula below [46].

$$\text{Quick 1} = \frac{1}{Log\ Insulin\mu U/ml + Log\ Glucose(mg/dL)}$$

Hence low levels of QUICK 1 have more risk for IR than higher values [45].

In 2013, Sneha *et al* involved anthropometric and biochemical markers of IR. They emphasized the relevance of simple anthropometric and biochemical indices such as body mass index (BMI), waist-hip ratio, fasting insulin, fasting glucose, fasting lipid profile and high sensitivity C-reactive protein (hscrp). These were all correlated with HOMA – IR by linear regression analysis. There were all positively correlated with HOMA-IR and they stated that these factors play major roles in IR and thus can serve as surrogate markers of IR [47].

Several other authors advocated the use of other biomarkers to assess IR viz: Oral glucose tolerance test [44, 48], glucose insulin product [49, 50], minimal model analysis of frequently sampled intravenous glucose tolerance test [51], fasting insulin [52], oral glucose insulin sensitivity test [53] and insulinogenic index [54].

7. Emerging Contemporary Markers

As the year, role by, multiple research works have confirmed certain break-throughs in the study of IR. They have incorporated several other markers of IR which have clinical applications. These range from simple analytes like lipids to HbA1C [55], resistin [56], sex hormone body globulin [57], adiponectin [58], ferritin [59], C-reactive protein(CRP) [60], high density lipoprotein(HDL) [60], Insulin growth factor binding globulin [62], triglycerides [63], and tumor necrosis factor alpha [64], soluble CD 36 [65], C3 complement [66].

IR can be investigated by various complementary techniques which are based on contemporary technologies. These include biopsy techniques, tissue micro analysis techniques, nuclear magnetic resonance, spectroscopy, positron emission tomography and insulin receptor binding studies. Another measure of insulin resistance is the modified insulin suppression test which correlates well with the euglycemic clamp, with less operator-dependent error. This test has been used to advance the large body of research relating to the metabolic syndrome [67]. Another factor that may promote insulin resistance is leptin, a hormone produced from the ob gene and adipocytes [68]. Leptin replacement in mice with obesity and diabetes has been found to quickly decrease glucose and insulin levels and can affect insulin sensitivity [69].

These have explored new ways of assessing IR with high level of success. It is hoped that with the advancement in medical research, more markers of insulin resistance will be discovered that will help in patient management.

8. Conclusion

This study aims to assess IR from origin till date with a view to assessing contemporary markers in the diagnosis of IR which are exploited in clinical management of patients. It is hoped that as continuous researches go on, there will be refiniment of these markers to enhance their usefulness in clinical management of patients.

References

[1] Borad A. Assessing insulin resistance: Clinical laboratory news of AACC. August 2016.

[2] Insulin resistance. In: www.wikipedia.com/insuilin resistance.

[3] Mohammed Al-far, Mohammed IM. Biochemical study of the effects of IR on sex hormones in men and women type 2 diabetic patients: *Advances in Biochemistry* 2017 S(5): 79 – 88.

[4] Sneha S, Rao S, Vidyasagar S. Anthropometric and Biochemical markers of insulin resistance. *International Journal of Science and Research*. 2016: 442 – 924.

[5] Kipres MS, Kronick A, Rendell MS, Egan JW, Mathisen AL. Pioglitazone hydrochloride in combination with Sulphonyurea therapy improves glycemic control in patients with type 2 diabetic mellitus. A randomized placebo-controlled study. *Am J. Med.* 111:10 – 17, 2007.

[6] Singh, B, Sexena A. Surrogate marker, of insulin resistance: A review *World Journal of Diabetes*: 15:1(2):36-47, 2010.

[7] Reaven GM, Banting Lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37: 1593 – 1607, 1988.

[8] Muniyappa R, Lee S, Chou H, Quon MJ Current approaches for assessing insulin sensitivity and resistance in viro: advantages, limitations and appropriate usage. *Am J physical Endocrinol Metab*. 2008; 294(1) E 15 – 26.

[9] Harrigan RA, Nathan MS, Beattle P. Oral agents for the treatment of type 2 diabetes mellitus: Pharmacology, toxicity, and treatment. *Annals of Emergency Medicine* 2001.38(1): 68-78.

[10] Reaven GM. The insulin resistance syndrome: Definition and dietary approaches to treatment. *Annu Rev. Natl.* 25: 391-406, 2005.

[11] Defranzo. RA, Ferranini E. Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, Hypertension, dyslipidemia and atherosclerotic cardiovascular disease.

[12] Petersen KF, Dufour S, Savage DB, Bilz S, Solomon G, Yonemitsu S. E. 2007. Inaugural lecture article: The role of skeletal muscle IR in the pathogenesis of the metabolic syndrome. *Proct Natl Acad Sci,* USA. 104: 12587 – 12594, 1997.

[13] Borai A, Livingstook C, Ferns GA. The biochemical assessment of insulin resistance. *Annals of Cinical Biochemistry* 2007; 44: 324–342.

[14] Krauss RM. Lipids and Lipoproteins in Patients With Type 2 Diabetes *Diabetes care* 2007; 44; 314 – 342.

[15] Greave J. Inhibition of the synthesis of apolipoprotein B containing lipoprotein. *Hand Exp Pharmacol* 2005; 170: 483 – 617.

[16] Lee JM Choudlury RP. Prospects for atherosclerosis regression: HDL elevation and other emerging therapeutic technologies. *Heart*: 2007, 93: 559 – 64.

[17] Marakmaan P, Dietary treatment of thrombogenic disorders related to the metabolic syndrome. *Br J Nutr* 2000; 83 (Supp 1): S 121 – 6.

[18] Kahn BB, Flier JS. Obesity and insulin resistance *The Journal of Clinical Investigations* 2001: 7412: 1108 – 16.

[19] Ginsberg HN. Insulin Resistance and Cardiovascular disease. *J. Clin. Invest.* 2000, 106: 453 – 8.

[20] Lillioja S, Moh DM, Howard BV, BemoHpH. Impaired glucose tolerance as a disorder of insulin action: longitudinal cross sectional studies in Pima Indians. *N Engl Med*. 1988. 318(19): 1217 – 1228.

[21] Wills, J, Watson JM, Hales CN, Phillips DI. The relation of fetal growth to insulin secretion in young men. *Diabet Med* 1996; 13: 773 – 4.

[22] Haring H, Obermaier B, Ermel B, et al. Insulin receptor kinase defects as a possible cause of cellular insulin resistance. *Diabetes Metab* 1987; 13:284 – 93.

[23] Innes, KE, Wimsatt JH. Pregnancy-induced hypertension and insulin resistance: evidence for a connection. Acta Obstet Gynecol 1999; 78:263 – 84.

[24] Maron DJ, Fair JM, Haskell WL. Saturated fat intake and insulin resistance in men with coronary artery disease. The Standford Coronary Risk Intervention project investigations and stuff. *Circulation* 1991: 84: 2020 – 7.

[25] Gustat J, Elkasabany A. Srinivasan S, Berenson GS. Relation of self-rated measures of physical activity to multiple risk factor insulin resistance syndrome in young adults: The Bogulusu heart study. *J. Clin. Epidemiol* 2002; 55: 997 – 1006.

[26] Kernielli E, Cohem P, Barzilai N. et al. Insulin resistance in Cushings syndrome. *Horm. Metab Res* 1985: 17: 518 – 21.

[27] Raza SA, Dewitt RT, Chan H, Warner TF, Blank RD. Catecholamine excess in phaecromocytoma inducing insulin resistance. *Endocr Pract* 2004: 149 – 52.

[28] Apridonidze T, Essah PA, Iwomo MJ, Nestler JE, Prevalence and characteristic of the metabolic syndrome in women with polycystic ovary syndrome. *J. Clin. Endocrinol Metab*.2005; 90: 1929 – 35.

[29] Ferrannini E, Buzzigoli G, Bonadonna R, et al. Insulin resistance in essential hypertension. *N Engl J. Med* 1987; 317: 350 – 7.

[30] Sam S. Obesity and Polycystic ovary Syndrome. *Obes Manag* 2007; 3(2):69-73.

[31] Rojas J, Chavez M, Olivar L, Rojas M, Morillo J. Insulin resistance and obesity: Navigating the pathophysiologic labyrinth *Int J Reprod Med 2014:719050.*

[32] Dunaif A. Insulin resistance and the polycystic ovary system. mechanism and implications for pathogenesis. *Endocr Rev* 1997; 18(6):774-800.

[33] Romo A, Benavides S. Acanthosis nigricans associated with insulin resistance: *Pathophysiology* and management. *Am J Clin Dermatol.* 2004; 5:199–203.

[34] Hermans – Le T, Scheen A, Pierard GE. Acanthosis nigricans associated with insulin resistance: Pathophysiology and management. *Am J Clin. Dermatol* 2004; 5(3): 199 – 203.

[35] Jaquest D, Tregouet DA, Nicacud V, Godefroy T. Combined effects of genetic and environmental factors on insulin resistance associated with reduced fetal growth. *Diabetes* 2002; 51(12): 3473 – 3478.

[36] Kahn R. Weight gain and insulin therapy. *British Journal of Diabetes and Vascular Disease*. 2004; 4(4): 264-267.

[37] Eckel RH. Lipoprotrin lipase A multifunctional enzyme relevant to common metabolic diseases. *N Engl J Med*. 1989, 320: 1060 – 1068.

[38] Reinehr T, Andler W. Cortisol and its relation to insulin resistance before and after weight loss in obese children. *Horn Res.* 2004; 62(4): 107 – 12.

[39] Aronoff, SL, Berkowitz K, Shreiner Barb, Want L Glucose Metabolism and Regulation: Beyond Insulin and Glucagon.. *Diabetes Spectrum* 2004 Jul; 17(3): 183-190.

[40] Defronzo RA, Bonadonna RC, Ferrannimi E. Pathogenesis of NIDDM: A balanced view – *Diabetes Care*. 1992; 151; 318 – 368.

[41] Greenfield MS, Doberne L, Kraemer F, Tobey T, Reaven G. Assessment of insulin resistance with insulin suppression test and the euglycemic clamp. *Diabetes* 1981: 30(5): 387 – 92.

[42] Matthew Dr, Hosker JP, Rudenski AS, Naylor BA, Turner RC. Homeostastic model assessment. Insulin resistance and beta cell function from fasty plasma, glucose and insulin concentration in man. *Diabetologic* 1985, 28: 412 – 419.

[43] Arora S. Surrogate markers of insulin resistance: A review. *World Journal of Diabetes.* 2010: 15(2) 36 – 47.

[44] Duncan MH, Singh BM, Wise PH, Carter G. A simple measure of insulin resistance. *Lancet* 1955, 346: 720 – 121.

[45] Matthew KJ, Hunt AE, Steinberg HO, Paradisi, G. Repeatedly characteristic of simple indices of insulin resistance: implications for research applications. *J Clin Endocrinol Metab* 2001, 86: 5457 – 5464.

[46] Sneha S, Sudhaker R, Vidyasugar Anthropometric and Biochemical markers of insulin resistance: *IJSR* 2013, 922 – 923.

[47] Hsieh CH, Kuo SW, Hung XJ, Shen DC HO CT. metabolic characteristics in individuals with impaired glucose homeostasis. *Int. J. Clin. Pract*. 2005; 59:639 – 644.

[48] Levine R, Haft DE, Carbohydrate Homeostasis. *N Eng J Med* 1970: 283: 287 – 246.

[49] Myllnen P, Koivisto VA, Nikkila EA. Glucose intolerance and insulin resistance accompany immobilization. *Acta Med Scand* 1987, 222: 75 – 81.

[50] Bergman RN, Ider YZ, Bowden CR, Cobelli, Quantitative estimation of insulin sensitivity.

[51] Consensus Development conference on insulin resistance. November 1997. American Diabetes Association. *Diabetes Care.* 1998. 21: 310 – 314.

[52] Mari, A, Pacini G, Murphy E, Ludrik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the cool glucose tolerance test. *Diabetes Care*. 2001, 24: 539 – 548.

[53] Goedecke JH, Dare JA, Faulenbaeh MV. Insulin response in relation to insulin sensitivity: an appropriate beta – cell response in black South African women. *Diabetes Care* 200, 32: 360 – 865.

[54] Osei K, Rhinesmith S, Gaillerd T, Schuster D. Is glycosylated haemoglobin AIC a surrogate for metabolic syndrome in non diabetic, first degree relation of African – American patient with type 2 diabetes. *Clin Exdocrinol Metab* 2003, 88: 4596 – 4601.

[55] Hivert MF, Sullivan IM, Fox CS, Nathan DM. association of adiponection, resisting and tumor necrosis factor alpha with insulin resistance. *J Clin Endorinol Metab* 2004; 89: 87 – 90.

[56] Kajaia N, Binder H, Diitrieh R, Oppelt PG, Flor B, Cupisti S, Low Sex hormone binding globulin as a predictive marker for insulin resistance in women with hyperandrogenic syndrome. *Eur J Endocrinol* 2007:157:499 – 507.

[57] Higashiura K, Ura N, Ohata J, Togashi N Takagi S. Correlation of adiponectin level with insulin resistance and atherosclerosis in Japanese male populations. *Clin Endocrinol* 2004, 61: 753 – 759.

[58] John M, Clark JM, Gundlar E. Serum ferritin and risk of the metabolic syndrome on US adults. *Diabetes Care* 2004: 27: 2422 – 2428.

[59] Pham NM, Nanri A, Kurotani K, Akter S, Foo LH, Nishi N. Serum ferritin is associated with markers of insulin resistance in Japanese men but not in women. *Metabolism* 2013.6(24):561-7

[60] Meng YX, Ford ES, Li C, Quarshe A. Al-Mahmoud AM, Giles W. Association of C – reactive proteins with surrogate measures of insulin resistance among non-diabetics from US from National Health and Nutrition Examination Survey. 1999 – 2002, *Clin Chem* 2007, 53: 2152 – 2159.

[61] Cordero A, Alegria- Ezquerrra E. TG/HDL ratio as surrogate marker for insulin resistance *ESC Council for Cardiology Practice 2009, 8(16).*

[62] Motaghadi R, Guijral S, Sinha S, Sison C, Ten S, Macleran NK. Insulin-like growth factor binding protein to screen for insulin resistance in children. *Diabetes Technol Thor* 2007, 9: 43 – 51.

[63] Glueck CJ, Khan NA, Umar Mohammad, Uppal MS, Ahmed W. Insulin resistance and triglycerides. *Journal of Investigative Medicine* 2009; 57: 874-881.

[64] Zinman B, hanley AJ, harris SB, Kwan J, Fantus IG. Circulating tumor necrosis factor alpha concentration in a native Canadaian population with high rates of type 2 diabetes in older men and women: The hoorn study. *J Clin Endocrinol Metab* 1999; 84:272-278

[65] Handberg A, Levin K, Hojlund K. Identification of the oxidized low-density lipoprotein scavenger receptor CD36 in plasma: a novel marker of insulin resistance. *Circulation* 2006; 114: 1169 – 1176.

[66] Muscari A, Antonelli S, Bianchi G, Cavrini G, Dapparto S, Ligabue. Serum C3 is a stronger inflammatory marker of insulin resistance than C – reactive protein leucocyte, and erythrocyte sedimentary rate: Comparison study in an elderly population. Diabetes Care, 2007: 30: 2362 – 2368.

[67] Muniyappa R, Lee S, Chen H, Quon MJ (January 2008). "Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage". American Journal of Physiology. Endocrinology and Metabolism. 294 (1): E15–26.

[68] Friedman JM (April 2000). "Obesity in the new millennium". Nature. 404 (6778): 632–4.

[69] Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM (July 1995). "Weight-reducing effects of the plasma protein encoded by the obese gene". Science. 269 (5223): 543–6.