

## **Review Article**

# **A Review of Contemporary Markers of Insulin Resistance**

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**Abstract:** Background: 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 as Google scholar, Hinari, Ebsco, Scopus, 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

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## **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 phaeochromocytoma [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 hypertriglyceridemia) 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 %  $\beta$  respectively) from fasting insulin and fasting glucose samples. It has 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].

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

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

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].

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

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 binding 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 refinement of these markers to enhance their usefulness in clinical management of patients.

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