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Unveiling the Hidden Risk: Insulin Resistance in Metabolically Obese Normal-Weight Individuals

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Abstract: Metabolically Obese Normal Weight (MONW) population is rather uninvestigated. Even if they fall into the normal BMI, these people have a number of metabolic risk factors similar to those of obesity such as insulin resistance. In this paper, detailed explanations of insulin resistance in MONW individuals, that makes up the background for developing type 2 diabetes, cardiovascular disease, and the metabolic syndrome, are explored. We focus on revealing phenotypic signatures that comprise MONW subjects, including increased visceral fat and low physical activity with abnormal lipid profile associating with BMI within the normal range. This paper also looks at some of the current diagnostic issues/contemporary and future implications on metabolic health and major issues of public health and argues for a reorientation of the understanding of metabolic health. The review discussed details and evidence of clinical trials to support the conclusion that and more elaborate metabolic assessing tools to diagnose and address insulin resistance in this vulnerable population are required.

Keywords: Metabolically Obese Normal Weight (MONW), Insulin Resistance, Visceral Adiposity, Metabolic Syndrome, Cardiovascular Risk, BMI Misclassification, Metabolic Dysregulation, Type 2 Diabetes

Introduction:

Insulin resistance is a pathological state which involves the inability of insulin to facilitate the movement of glucose into the cells and thus leading to increased levels of blood glucose and susceptibility to developing type 2 diabetes mellitus (T2DM) and other diseases of metabolic origin[1]. It is found in metabolic syndrome which is a group of factors such as central obesity, hypertension, high level of cholesterol and impaired glucose tolerance[2]. Conventionally, it has been postulated that obesity was a cofactor of insulin resistance where the accumulation of excess body fat especially in the abdominal region leads to development of the condition[3]. However, there is a group of people, called Metabolically Obese Normal Weight (MONW), to whom this notion is attributable, nevertheless, these patients exhibit metabolically abnormal phenotype[4]. Our goal is to present general information about insulin resistance in MONW people, such as the frequency of its occurrences, geographical and gender factors, molecular processes leading to this condition, and its consequences.

The proportion of MONW people who have insulin resistance has increased, demonstrating deviation from the classic Body Mass Index (BMI) approach to defining obesity. The latter is based on statistics reported by the National Health and Nutrition Examination Survey (NHANES) in the United States that reveals that roughly 20% of people with a normal weight (by the BMI scale of 18. 5–24. 9 kg/m²), suffer from metabolic markers that reflect insulin resistance and related disorders[5]. This is not a unique picture of the U. S. only but this is what can be seen in Europe and Asian countries too[6]. For instance, research on European populations have found out the same percentage of people with MONW, this shows that the vice is not restricted by geographical or demographic barriers[7].

This is particularly because insulin resistance has gained increasing prevalence in normal weight population especially in the developing countries due to factors such as increased rates of urbanization and changes in lifestyle[8]. Assimilation of high calorie diets, sedentary lifestyles especially in the urban areas as a result of modernization contribute to the storage of visceral fat and the consequent insulin resistance in apparently normal weight individuals[9]. Looking at the demographic situation, one can state that more attention should be paid to modern approaches that are more suitable for evaluating metabolic health than the plain BMI figures[10].

Molecularly, insulin resistance refers to a complicated altered in the pathway through which the insulin hormone operates. Insulin promotes the internalisation of glucose into the various cells by targeting the insulin receptor thus triggering an intracellular signalling including the insulin receptor substrate (IRS), phosphatidylinositol 3 kinase (PI3K) and protein kinase B (Akt)[11]. In insulin resistance, these signaling molecules are dysfunctional and affect these processes in such a way that glucose uptake is sharply reduced and hyperglycemia results[12].

In MONW individuals, it was found that there exist a molecular alteration that leads to insulin resistance although these individuals possess a normal BMI[13]. One is adipokines which are bioactive peptides released from adipocytes tissues, A list of some adipokines includes; Major adipokines that are linked to insulin resistance include resistin, leptin and adiponectin[14]. For example, resistin which is secreted by adipose tissue interferes with insulin signaling and causes inflammation and thus enhance the extent of insulin resistance. The adipokine leptin which is usually raised in obesity can also induce peripheral insulin resistance through its actions at the level of the brain and on insulin-signaling system[15]. On the other hand, adiponectin is an adipokine that has insulin sensitizing function and is reported to be reduced in MONW people so playing a role in metabolic disorder.

Another issue that relates to obesity is the ability of excess visceral fat to affect insulin levels. Anthropometric measurements of this fat tissue, located around the internal organs, indicates that this fat is more bioactive compared with subcutaneous fat that secretes inflammatory cytokines such as TNF-α AND IL-6[16]. These cytokines impair signal transduction pathways of insulin and also increase inflammations in the body

making insulin resistance worse. Notably, this accumulation of visceral fat is not always expressed with increased BMI because the later measures overall body weight and not the composition of the fat pad.

Inflammation and oxidative stress also play their part in the development of the insulin resistance in MONW individuals. Inflammation that is characterised by low-grade, and particularly if catalysed by visceral fat, results in pro-inflammatory cytokines being produced that interfere with insulin signaling[17]. Furthermore, increase production of reactive oxygen species (ROS), which leads to oxidative stress and disturbed balance between the generation of these products and antioxidant protection intensifies cell injury and insulin resistance. Higher accumulation of ROS can cause insults to cellular structures such as lipids, proteins, and DNA, which all play an important role in the development of insulin resistance[18].

Thus, the presence of insulin resistance in MONW subjects supports the inadequacy of BMI for evaluating metabolic health. BMI, weight divided in kilograms by height in meter square has lack of appreciation of differences in muscle mass and fat topography. In that case, normal weight BMI people with a high percentage of body fat, especially visceral adipose tissue, fall in the category of having a healthy metabolism when in fact they are at high risk for metabolic diseases.

Due to such a complexity of the problem for identifying Insulin Resistance (IR) in MONW individuals, it is needed to perform a more integrated approach to the assessment. This involves assessing the distribution of body fat through other technological imaging methods like the Dual-energy X-ray absorptiometry (DXA) scans and computed tomography (CT) scans[19]. DXA offers percentage analysis of fat mass and fat free mass and CT offers the measurement of visceral fat area. Further, biomarkers of inflammation and oxidative stress, that are protein and lipid markers, can provide a better understanding of the metabolic profile of MONW individuals.

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is well known indices used for the assessment of insulin resistance. HOMA-IR is obtained from data fasting insulin and glucose levels which gives an indication of insulin sensitivity[20]. As valuable as HOMA-IR might be, to make a more precise conclusion about patients ' metabolism, it is better to use it in combination with other diagnostic indicators.

Public Health and Preventive Strategies

The fact that MONW individuals are recognized enforces the need to focus on the specific prevention and health promotion activities. Therefore, programs aimed at the early diagnosis and treatment of insulin resistance in such patients is important in order to avoid the development of other metabolic complications such as type 2 diabetes. People should be informed that BMI has its flaws while health policies should encourage metabolic evaluations that incorporate body fat location and biochemical tests.

There is no doubt that changes in life style are the cornerstones in the management of insulin resistance. These include physical activity, a diet rich in whole foods, and weight control that are effective preventive measures. Studies have proved that, even small changes in our daily habits greatly enhance the insulin sensitivity and decrease the probability of metabolic diseases[21]. Preventive measures should be directed toward raising people's awareness of the need for such changes in their diet and offering guidance with the implementation of these changes.

Healthcare providers should be educated on the reality that BMI cannot provide a full of picture of someone's health status and should be backed by other diagnostic approaches. Therefore, understanding the aspects of metabolic health separately will help the healthcare experts to include proper assessment and targeted treatment approaches for the high-risk population.

Thus, the study of insulin resistance in MONW individuals is a major unexplored concept in metabolic health. It suggests that the use of BMI to quantify obesity and metabolic risk, which is traditional, is not enough to separate people at risk for excessive metabolic disorders among those who have normal weight. Further, evaluations of body adiposity, inflammatory and oxidative stress indexes, and novel diagnostic techniques are crucial for a correct diagnosis of overall IR in such subjects[22]. Given that metabolic disorders have become increasingly common all over the world, it will be important to handle the problems associated with MONW individuals in order to promote public health and enhance knowledge in the area of metabolic diseases.

Molecular and Cellular Mechanisms

In order to understand molecular and cellular origins of insulin resistance in MONW individuals, one has to discuss numerous biological pathways and their potential interrelations. Implicit in this notion is the issue of insulin signaling cascade and how disruptions within can be expressed in people without diabetes.

1. Insulin Signaling Pathway Disruptions

Aetiology of insulin resistance starts with changes in the insulin signaling pathways. Usually, insulin attaches to the insulin receptor and this activates the IRS proteins which are followed by phosphorylation process that facilitates the glucose transport. In MONW individuals, this pathway is not active. Namely, IRS-1/-2 phosphorylation might be decreased such that their capacity to activate subsequent targets, for instance, PI3K and Akt, is impaired[23]. This suppressed activation fails to translocate glucose transporter (GLUT4) to the cell membrane for glucose uptake and consequently hyperglycemia ensues.

2. Role of Adipokines

As pointed out earlier, adipokines have important roles to play in regulation of insulin sensitivity and things as such. Leptin a cytokine synthesized mainly by adipose tissue, is involved in the regulation of energy intake and energy expenditure as well as it plays a significant role in insulin signaling[24]. In MONW individuals, there is leptin

resistance by which the normal signaling by leptin is disrupted in spite of the high levels of the hormone[25]. It has been suggested that this resistance leads to alteration of the central regulation of glucose homeostasis thereby increasing insulin resistance.

On the other hand adiponectin has been associated with insulin sensitization On the other hand adiponectin has been associated with insulin sensitization. It has been established that MONW individuals have low adiponectin level and this is associated with poor insulin sensitivity. Adiponectin promotes fatty acid oxidation as well as glucose uptake into cells and its deficiency plays an important role in the development of metabolic derangement in MONW population.

3. Inflammation and Oxidative Stress

Pro-inflammatory state is considered as a potential mechanism for development of insulin resistance. The MONW individuals were found to have low grade chronic inflammation in most cases. High C-Rwactive Protein (CRP) and increased concentration of pro-inflammatory cytokines including Tumor necrosis Factor Alpha (TNF-α), and Interleukein-6 (IL-6) have been linked to reduced responsiveness to insulin[26]. These cytokines can trigger inflammation cascade like nuclear factor-kappa B (NF-κB) which in turn impairs insulin signaling and cause inflammation to occur all over the body.

Another factor involves the oxidative stress which has contributed much to the entire disease. Oxidative stress alters the components of cell signaling and impairs function through oxidative alteration of components in the insulin signaling pathway. As can be seen in the present study, ROS can blunt the insulin receptor function in MONW individuals along with the existing inflammatory scenario.

4. Genetic and Epigenetic Factors

Other causes of insulin resistance in MONW population include genetic factors and epigenetic changes. Further, there are other genes such as TCF7L2, FTO, and PPARG that when mutated have been found to cause insulin resistance and therefore result in metabolic disorders even with normal BMI[27]. Some of these genetic differences may perturb insulin action, glucose handling, and adiposity.

This is also true for epigenetic modifications that are other chemical modifications of DNA. The latter means that the molecules that form chromosomes can have their genes turned on or off through the processes of DNA methylation and histone modifications, in other words, gene expression without changing the genetic instructions. Some of these changes may affect the regulation of insulin responsive genes, adipogenic genes, and genes implicated in inflammation thereby playing a role in shaping metabolic profile of MONW people.

Clinical Implications and Management Strategies

The consequences which insulin resistance has on the clinical management of MONW subjects are staggering. This condition is very vital to know because when persisted it results to type 2 diabetes and other metabolic complications. That is why, using BMI as the only parameter for classification and evaluation of patients often leaves Patients with metabolic abnormalities and normal weight.

Accordingly, for enhancing the level of the diagnosis of insulin resistance among MONW individuals the paradigm of diagnosis should rely on a combination of approaches. This includes:

- Advanced Imaging Techniques: BMI is not sufficient to show the distribution of body fat especially the visceral fat and a DXA and a CT scan can accomplish this.
- Biomarker Assessments: Assessment of Inflammatory proteins, products of oxidative stress and adipokines may provide such other information about the metabolic status of the person.
- Functional Tests: However, other methods such as glucose tolerance tests and euglycemic–hyperinsulinemic clamp studies offer better evaluation of the same.

Effective management of insulin resistance in MONW individuals focuses on lifestyle modifications:Effective management of insulin resistance in MONW individuals focuses on lifestyle modifications:

- Physical Activity: This ensures that your body insulin sensitivity improves as well as helps in reducing fat in specific areas like the visceral fat body area. Aerobic and resistance exercise training has been known to be favorable.
- Dietary Modifications: A diet that has been evaluated for its fiber, fats and proteins should be encouraged for metabolic health. One of the best ways of managing diabetes involves cutting down the consumption of refined sugars and processed foods.
- Weight Management: MONW individuals may not be required to lose considerable amount of weight, but mere weight loss coupled with reduction of body fat can make a big difference in regards to insulin sensitivity.

Sometimes a sole reliance on the lifestyle interventions proves to be ineffective. Pharmacological treatments can complement lifestyle changes, including: Pharmacological treatments can complement lifestyle changes, including:

- Metformin: The most prescribed antidiabetic drug in the first-line treatment of IR and T2DM, metformin, assists in enhancing the overall insulin responsiveness and glycemic profile[28].
- Thiazolidinediones: These drugs produce insulin sensitisation due to increased binding of peroxisome proliferator-activated receptor- gamma (PPAR- γ)[29].

- GLP-1 Receptor Agonists: These agents enhance the ability of cells to take up glucose and therefore they reduce central obesity[30].

More research is therefore required to further elaborate on the issue to do with Insulin Resistance in MONW people. Key areas for exploration include:Key areas for exploration include:

- Longitudinal Studies: It is possible to use MONW individuals to see the changes that take place with regard to insulin resistance and the development of metabolic disorders.
- Mechanistic Studies: Studying the molecular and cellular changes unique to MONW people will enable the identification of new therapeutic avenues.
- Intervention Trials: Learning about the efficiency of different lifestyle and pharmacological approaches in the MONW population can help to optimise the management process.

Discussion :

Insulin resistance in metabolically obese but normal-weight (MONW) people is one of the key problems that must be solved to explain metabolic health. Despite normal weight reflected by BMI scale, monogenic overweight subjects have several features of obese people, the most important of which is insulin resistance. This paradox underlines the problem of using BMI as the sole indicator of metabolic health, since it fails to take into consideration even differences in adipose tissue distribution.

Sometimes BMI plays the role of a marker of obesity; it compares the weight of the person to his height and is connected with the evaluation of the metabolic risk. Nevertheless, it is a major drawback of BMI because it fails to distinguish between fat mass and fat-free mass thereby its usefulness in screening out people with metabolic disorders. For example, Romero-Corral et al. stressed that people with normal BMI and high adiposity have a higher chance to experience metabolic syndrome than those with high BMI but low fat[31]. Along the same line, Mottillo et al. showed that excess body fat that exists in normal-weight people predisposes them to adverse metabolic effects[32]. Thus, these reports emphasise the need to consider other indicators in the study of metabolic health aside from BMI.

Of all these fats, Visceral fat is known to have a close connection with insulin resistance. Another type of fat is visceral fat and as the name suggests it is lodged around internal organs and is considered to be of very high metabolic activity. This induces the production of inflammatory cytokines and adipokines that dysregulate insulin signaling hence the defective glucose homeostasis. Kahn and Yoon have also done research to show that, accumulation of visceral fat causes inflammatory response and oxidative stress, which are precipitated causes of insulin resistance[33]. This view is also supported by the study conducted by Després et al which also revealed that whilst Visceral fat is associated with metabolic syndrome, actual body weight cannot sufficiently predict this condition[34].

Physical activities and cardiorespiratory endurance are also among the important parameters that have an effect on insulin resistance within MONW individuals. Decreased engagement in physical activities and diminished cardiorespiratory endurance have been related to increased visceral fat deposition and metabolic derangement. Lavie et al. have observed that high insulin resistance and metabolic disorders risks are frequent with low physical activity levels[35]. Such a relation is supported by Ekelund et al.'s study which pointed out the beneficial effect that exercise had on insulin sensitivity[36]. These findings suggest that physical activity improvement may lower the metabolic concerns that accompany MONW.

These mechanistic aspects of MONW patients 'insulin resistance include genetic, hormonal, and environmental variables that interact in a complex manner. Insulin resistance is caused by altered insulin signaling which prevents cellular glucose uptake. There are increased free fatty acids in the circulation as a result of visceral obesity which adds to this dysfunction by causing inflammation and oxidative stress[37]. Shulman et al. have highlighted mechanisms through which elevated free fatty acids act to impair insulin receptor signaling thus increasing the rate of insulin resistance[38].

Genetic elements also play a function within the improvement of MONW. Several genetic markers had been associated with obesity and insulin resistance, together with variants within the FTO gene. Loos et al. Diagnosed that genetic versions in FTO are related to expanded frame fat and insulin resistance[39]. This finding is supported by means of a look at by way of Yeo et al., which established that genetic predisposition contributes notably to the improvement of metabolic problems in people with normal weight[40].

The scientific implications of recognizing and handling MONW are full-size. Early detection of MONW individuals lets in for timely interventions to prevent the progression to type 2 diabetes and cardiovascular illnesses. Tailoring interventions to deal with the precise metabolic profile of MONW individuals is vital. Lifestyle adjustments, which include extended bodily activity and dietary changes, were proven to enhance insulin sensitivity and decrease frame fat on this population. The Diabetes Prevention Program proven that way of life interventions may want to drastically decrease the risk of kind 2 diabetes in high-danger individuals, which include people with regular weight however expanded frame fat[41]. Additionally, the Look AHEAD examine discovered that weight loss and extended physical interest improved insulin sensitivity and reduced the risk of metabolic disorders in overweight and obese individuals[42].

Several different research have contributed to the knowledge of MONW and its management. For instance, a observe by Cnop et al. Highlighted that MONW individuals have higher visceral fats and insulin resistance in comparison to their metabolically healthy opposite numbers, emphasizing the want for centered interventions[43]. Furthermore, research via Lim et al. Discovered that MONW individuals are at elevated hazard for cardiovascular diseases due to their insulin-

resistant country, even when their BMI is within the everyday variety[44]. These studies collectively improve the significance of considering frame composition and metabolic health past conventional BMI measurements.

In end, the discussion on insulin resistance in MONW individuals underscores the constraints of BMI as a measure of metabolic fitness and highlights the want for a extra nuanced technique to comparing metabolic threat. By thinking about elements such as visceral fats, bodily activity, genetic predisposition, and molecular mechanisms, healthcare professionals can higher deal with the complexities of MONW. Future studies ought to awareness on refining diagnostic criteria, growing focused interventions, and enhancing the management of metabolic issues in this at-risk population.

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