Metabolic Syndrome or Insulin Resistance: Evolution, Controversies and Association With Cardiovascular Disease Risk

Arun K. Chopra

Abstract
Metabolic syndrome is a clinical entity characterized by abdominal obesity, atherogenic dyslipidemia, impaired glucose tolerance, and hypertension (HT). Despite various attempts at definition, the syndrome has remained mired in controversy over its components and utility. Insulin resistance and its association with risk of cardiovascular disease are discussed at length in this article.

This review also discusses the controversies in the definition of this syndrome, the unique role of insulin resistance in its development, and the causes and implications of this clustering of risk factors characteristic to it, along with suggestions for a more comprehensive approach to this common problem.

Keywords
Atherogenic dyslipidemia, insulin resistance, metabolic syndrome, obesity

Introduction
Metabolic syndrome (MetS) is a constellation of abnormalities including abdominal obesity, atherogenic dyslipidemia, prediabetes, and hypertension (HT), with its own classification code and at least 7 sets of guidelines to define it.1,3-9 Despite this, there continue to be controversies regarding its definition, and its founder and other groups have published negative reviews repeatedly, vehemently questioning its validity. Why is MetS so exciting and yet so controversial?

This review attempts to summarize the concept and evolution of MetS, the controversies and challenges that surround it, its association with cardiovascular disease (CVD) risk and suggests future actions.

What Is the Controversy Regarding the Definition of MetS?

The concept was first formalized by Professor Gerald Reaven at the 1988 Banting Lecture where he presented data suggesting that insulin resistance (IR) was the underlying common factor behind several related clinical and biochemical abnormalities that predisposed to diabetes, hypertension, and coronary heart disease (CHD).1 He suggested the moniker Syndrome X or Insulin Resistance Syndrome (IRS) for this condition (Table 1), which was characterized by minor degrees of glucose intolerance (on oral glucose tolerance test [OGTT] in healthy nondiabetic subjects), dyslipidemia, endothelial dysfunction, a procoagulant and pro-inflammatory state, hemodynamic changes, and abnormal uric acid metabolism, thus predisposing individuals to type 2 diabetes (T2D), CVD, essential hypertension, polycystic ovary syndrome (PCOS), and nonalcoholic fatty liver disease.2

The first attempt at definition of a clinical syndrome was made by the World Health Organization in 1998 to identify these high-risk individuals and intervene early in order to reduce the associated morbidity and mortality.3 Several other associations came out with modifications within the next decade, the aim being a definition that was simple, yet comprehensive; a consensus statement was issued in 2009.4

The evolution of this definition is responsible for much of the prevailing controversy as to the utility of this concept: while the World Health Organization, European Group for the Study of Insulin Resistance (EGIR), and American Academy of Clinical Endocrinologists (AACE) proposed

1 Fortis Escorts Hospital, Amritsar, Punjab, India
Corresponding author:
Arun K. Chopra, Fortis Escorts Hospital, Amritsar, Punjab 143004, India.
E-mail: akchopra1@rediffmail.com

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definitions based upon obligatory evidence of IR (impairment fasting glucose [IFG], impaired glucose tolerance [IGT]), serum insulin levels, or type 2 diabetes), others such as National Cholesterol Education Program: Adult Treatment Panel III (NCEP:ATP-III), International Diabetes Forum (IDF), American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI), and the Consensus definition by IDF and AHA/NHLBI) have diluted IR itself in an effort to keep the definition simple and practical. The criteria for several reasons:

1. The idea behind defining the syndrome is unclear: The logic behind the syndrome is to predict the risk of T2D or CVD; however, as presently defined, it cannot be linked to a single underlying cause, nor does it encompass the entire spectrum of risk factors. Factor analysis studies by multiple teams have consistently encountered at least 2, and usually 3 or even 4 factors to be responsible. Most studies consider 3 overlapping factors (obesity, IGT, or central MetS, and dyslipidemia) rather than IR alone to be responsible for the entire spectrum of MetS. Moreover, approximately 78% of obese nondiabetic individuals with MetS in a study were IR; conversely, only 48% individuals with IR had MetS, confirming that MetS and IRS are not synonymous.22 Thus, the syndrome neither has common etiology nor serves as an efficient tool to predict CVD, and if the purpose is to diagnose IR, a high triglycerides (TG)/high-density lipoprotein cholesterol (HDL-C) ratio alone is a simpler and more sensitive indicator with better positive predictive value, even better are Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and body mass index (BMI) or BMI with family history of diabetes.20,23

2. The definition is cluttered: As it includes both the factors underlying IR (obesity) and its consequences (prediabetes, hypertension, and dyslipidemia). Furthermore, there are only cut-points for various values and no gradation of risk, as is used with other scoring systems. Waist circumference is the first criterion without any study showing its reproducibility in different ethnic groups, and with no evidence that it performs better than BMI, which is a more simple and practical measurement. The criteria are democratic, with no differentiation as to whether some risk factors may be stronger than others: all risk factors have significant association with CVD except obesity (whether total/subcutaneous/visceral fat), the strongest being hypertension and low HDL-C. Finally, risk factors that correlate strongly with IR have been excluded (C-reactive protein [CRP], adiponectin), while weaker correlates like hypertension are included.20

3. It does not fulfill its raison d’être: Though an efficient predictor of diabetes risk, it excludes several definite CVD risk factors (eg, age, smoking, family h/o CVD, low-density lipoprotein cholesterol [LDL-C]): the Framingham Risk Score (FRS) performs

**Table 1. Components of Syndrome-X**

| Insulin resistance: | Hyperinsulinemia |
| Mild degrees of glucose intolerance: | IFG, IGT |
| Atherogenic dyslipidemia: | Elevated triglyceride levels | Low HDL-cholesterol levels | Postprandial lipemia | sd-LDL cholesterol (pattern B) | Endothelial dysfunction |
| Proinflammatory factors: | Elevated C-reactive protein | Elevated uric acid, GGT, TNF-α, IL–6 |
| Prothrombotic factors: | Elevated fibrinogen levels | Elevated PAI–I levels |
| Hemodynamic changes: | Enhanced sympathetic nervous system activity | Excess sodium retention |

**Abbreviations:** GGT, gamma glutamyl transferase; TNF-α, tumor necrosis factor-α; IL–6, interleukin–6.

**Table 2. Clinical Syndromes Associated With Insulin Resistance**

| Type-2 diabetes |
| Essential hypertension |
| Cardiovascular disease |
| Nonalcoholic fatty liver disease |
| Polycystic ovary syndrome |

The diagnosis of MetS does confer higher risk of T2D and CVD upon affected individuals, with population-based studies finding that nearly one-sixth to one-third of adults of various populations globally qualify for this diagnosis. Its proponents suggest genetic susceptibility to the syndrome with excess body fat as the underlying etiology, and lifestyle modification leading to weight reduction as the cure: weight loss of approximately 11 kg brings about nearly 40% improvement in insulin-mediated glucose uptake (IMGU), contributing significantly to reducing IR and the associated biochemical abnormalities.

Despite the seeming consensus, there are several refined criticisms of this definition, both by Reaven himself and others. These question the very need for the syndrome for several reasons:

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better in predicting CVD risk (HR 1.5 vs. 7.9 with FRS). Thus, the sum (the syndrome as a whole) is not more important than its parts, prompting AHA to advise that finding any risk factor should prompt a search for others, and treatment as per clinical guidelines for individual conditions.\textsuperscript{14,17-20}

4. There is no specific therapy approved for IR or MetS: While insulin sensitizers are available, there is patchy evidence demonstrating any benefit in CVD or total mortality with these agents.\textsuperscript{20} Most trials included high-risk subjects with established T2D (PROactive, RECORD, DREAM, BARI–2D), and failed to reduce cardiovascular (CV) mortality, nonfatal myocardial infarction (MI) or stroke significantly. Only the insulin resistance intervention after stroke (IRIS) trial enrolling IR individuals with previous stroke evaluated the benefits of pioglitaxone and reported a 24% reduction in fatal/nonfatal stroke or MI. However, inconsistent benefits, reports of increased risk of weight gain, heart failure and bone fractures, and the availability of newer drugs with greater potential CV benefits (SGLT2 inhibitors, GLP1-RA) have served to minimize the clinical utility of thiazolidinediones.\textsuperscript{24,25}

In summary, the definition is far from resolved, the benefits of labeling the syndrome over individual risk factors are unclear or nonexistent, and there is no approved specific therapy other than the treatment of the individual conditions.

What Is Insulin Resistance?

IMGU is very variable in population, with insulin levels varying up to 6 to 8 times in healthy, nondiabetic subjects, as tested by hyperinsulinemic, euglycemic clamp studies.\textsuperscript{1,2,17,19} Another technique that is validated is the insulin suppression test (IST) performed using continuous infusions of octreotide, insulin, and glucose to establish stable plasma insulin and glucose levels; the steady-state plasma glucose (SSPG) concentration provides an estimate of glucose disposal related to the specified level of insulin infused: the higher the SSPG, the more IR the subject. These 2 techniques have excellent correlation in both normal subjects and in diabetics, both obese and nonobese ($r > 0.9$).\textsuperscript{12}

IR is complicated: studies using the IST have established that most subjects with T2D are IR; surprisingly, nearly one-fourth to one-third of the healthy, nondiabetic population also has an equivalent level of IR. The EGIR defines IR as the ninetieth percentile of insulin levels in nondiabetic, lean subjects, making 10% of the lean healthy population IR. This is obviously an arbitrary cutoff, though supported by clinical studies demonstrating an increased risk of CVD in as much as the upper tertile of fasting insulin levels.\textsuperscript{2,18,26}

Multiple studies have demonstrated the association of IR with prediabetes, atherogenic dyslipidemia (low HDL-cholesterol and/or elevated triglycerides), and hypertension.\textsuperscript{27-29} Many healthy individuals with apparently normal blood glucose levels also have IR and insulin levels that are similar to diabetic subjects.\textsuperscript{1,2} In these healthy individuals, the excess insulin secreted by the pancreas keeps blood glucose in check, but at the cost of elevated daylong insulin levels. It is when the pancreas fails to compensate for IR that clinical diabetes ensues. However, the persistently elevated insulin levels are not benign and result in the clinical and biochemical abnormalities mentioned earlier.\textsuperscript{1,2,17,18}

IR has multifactorial etiology (Table 3): nearly half is attributable to genetic factors, while the remaining half is related to lifestyle factors (nearly half of this is related to adiposity, about the same degree to physical activity, and variable degrees to stress, smoking, and alcohol).\textsuperscript{2,18,27,28}

Obesity is strongly correlated with IR, with increasing BMI predisposing to IR; however, there is no direct correlation between body weight (or visceral adiposity) and IR.\textsuperscript{2,18,27} As about 10% of lean individuals and one-third of obese individuals are IR, the total number of lean and overweight individuals with IR in population is nearly twice as much as obese individuals with IR, making the logic behind including obesity as a defining characteristic suspect.\textsuperscript{2,18,26} To complicate matters further, several populations are more IR than Europids, including South Asians and African-Americans even at normal BMI.\textsuperscript{1,2} The concept of lean MetS has also been proposed.\textsuperscript{31} Of note, studies have established that obesity predisposes to IR and is not caused by it.\textsuperscript{32}

What Are the Metabolic and Vascular Consequences of IR and Obesity That Link Them With CVD?

Multiple population-based studies suggest that CVD is more common in subjects with IR, and experimental studies have confirmed the association of several CVD risk factors with IR and obesity.\textsuperscript{24,29,33,34} Data from the NHANES-II revealed a 2-fold risk of CHD mortality with this diagnosis, though the risk was still higher in those with diabetes alone or previous CVD.\textsuperscript{11} The ARIC study investigators concluded that men and women were approximately 1.5 and 2 times more likely to develop CHD than control subjects, even after adjusting for age, smoking, LDL-C, and race.\textsuperscript{13} Another systematic

Table 3. Etiological Factors for Insulin Resistance (IR)

| Risk Factor   | Relative Contribution |
|---------------|-----------------------|
| Genetic factors | Approx. 50%           |
| Obesity       | Approx. 22-25%        |
| Physical inactivity | Approx 25%     |
| Stress        | Worsens IR            |
| Smoking       | Worsens IR            |
| Alcohol       | Moderate intake improves insulin sensitivity |

Note: Genetic factors are associated with insulin signaling.
review of 87 studies with 951,083 patients using NCEP and revised NCEP definitions concluded that there was significant increased risk of CVD (RR 2.35, 95% CI [2.02, 2.73]), CVD mortality (RR 2.4, 95% CI [1.87, 3.08]), all-cause mortality (RR 1.58, 95% CI [1.39, 1.78]), MI (RR 1.99, 95% CI [1.61, 2.46]), and stroke (RR 2.27, 95% CI [1.80, 2.85]). The risk was significantly higher in women than in men, especially for all-cause mortality (RR in women 1.86, 95% CI [1.37, 2.52], in men RR 1.42, 95% CI [1.16, 1.74]); the risk of CVD mortality decreased somewhat on excluding diabetes, but remained significant still (RR 1.75, 95% CI [1.19, 2.58]). This finding, and the fact that T2D is a potent standalone risk factor, has probably resulted in the removal of diabetes (and the inclusion of only IFG) as the criterion in the consensus definition.4,11

Like diabetes, MetS apparently eliminates the gender benefit with regard to CVD in females: the greater central adiposity, greater changes in lipids post menopause, stronger association of TGs with CVD risk, oral contraceptive use, gestational diabetes, and PCOS could be some of the factors responsible.34

The cellular actions of insulin suggest putative mechanisms for enhancing the risk of CVD and acute coronary syndromes. Insulin acts by binding to its receptors, which leads to the activation of 2 parallel pathways: the phosphoinositide 3-kinase (PI3K) pathway and the mitogen-activated protein (MAP) kinase pathway. The PI3K pathway mediates most of its metabolic actions like glucose uptake in skeletal muscle and adipose tissue (through glucose transporter GLUT4) and activation of endothelial nitric oxide synthase. The MAP kinase pathway mediates endothelin–1 (ET–1) production, vascular cell adhesion molecules (VCAM–1), and E-selectin, leading to its other effects on vascular endothelium including vasoconstriction, leucocyte-endothelial interactions, and mitogenic effects on vascular smooth muscle cells. Acting through these pathways, insulin has contrasting effects on vascular tone, with the balance being neutral or vasodilatation in normal individuals.35,36

In IR individuals, the PI3K kinase pathway is affected, while the MAP-kinase pathway is not: this change in the balance between the 2 leads to impaired glucose uptake by skeletal muscles and adipose tissue along with endothelial dysfunction due to reduction in endothelial nitric oxide synthase activity with continued ET–1 generation.35

Obesity predisposes to IR and vascular dysfunction probably through adipokines such as tumor necrosis factor alpha (TNF-α) and interleukin–6 (IL–6), which are proinflammatory, excess-free fatty acids (FFA), and through the activation of renin angiotensin system (RAS) that is expressed in adipose tissue (which may be predisposing to hypertension). Furthermore, adiponectin, a protective adipokine, is reduced in obesity, T2D, and MetS. These changes in the adipokines and excess FFAs that are released from visceral fat act together to impair the PI3K-Akt pathway, and increase the reactive oxygen species production as well as ET–1 release.36 Obesity (especially BMI) has been demonstrated to have direct correlation with blood pressure (BP) and the risk of hypertension,18,19,37,38 probably through RAS; blocking RAS with angiotensin converting enzyme inhibitors or angiotensin receptor blockers improves insulin sensitivity and reduces the risk of new-onset diabetes in hypertensive individuals by about 25%, as does weight loss. These drugs can also block the FFA-induced impairment of endothelial function discussed above, suggesting that they act through the RAS.36

Obesity and IR are strongly correlated: obese individuals (whether defined by waist circumference or BMI) had significantly higher SSPG (P < .001), glucose (P < .001), and triglycerides (TG) levels (P = .01) than nonobese subjects, whereas the total cholesterol, LDL-C or HDL-C, levels were similar. BMI showed a linear correlation with rising values of these parameters (BMI < 25, 25-29.9, and > 30).37

Despite this, data from NHANES-III suggests that obesity is not an independent predictor of CHD or total mortality.39 Another large meta-analysis of prospective studies in nearly a quarter million individuals from 17 countries also concluded that BMI, waist-to-hip ratio or waist circumference do not improve CVD risk prediction after accounting for systolic BP, diabetes, and lipids.41 Contrarily, fasting plasma insulin levels (as a surrogate marker of IR) have been repeatedly demonstrated to be an independent predictor of CVD risk in middle-aged males in different countries.2,28,29,33,40 These findings suggest that the elusive link between obesity and CVD could be IR, and studies support the view that one-fourth to one-third of an apparently healthy population maybe IR enough to be at higher risk of CVD.2,18

In order to evaluate the metabolic profile of obese individuals, Reaven et al divided 211 obese nondiabetic subjects into 3 groups based on their SSPG levels on the IST. The values of all established CV risk factors (except LDL-C) increased linearly depending upon the degree of IR. Thus, systolic and diastolic BP (P < .001), TGs (P < .001), HDL-C (P < .001), fasting and 2-hour plasma glucose during OGTT (P < .001), all had values that were significantly worse in the intermediate group in most parameters. This emphasizes that the levels of all risk factors for CVD are much lesser in the insulin-sensitive obese subjects than in the IR obese group. Of note, nearly half the subjects in the most IR tertile had IFG, compared to only 1% of the most insulin-sensitive group, suggesting that these one-third obese subjects were at low risk of diabetes, and possibly CVD as well. This also suggests that performing an OGTT (at least a plasma glucose level 2 hours after a 75 g oral glucose load) in all overweight or obese individuals while evaluating their risk status may be particularly useful, as two-thirds of the individuals in the uppermost SSPG tertile had IGT.42

Persistent IR with hyperinsulinemia increases the risk of prediabetes and T2D (though nearly one-fourth of the subjects...
with high insulin levels are insulin sensitive, while one-fourth of IR individuals have insulin levels in the normal range. Studies suggest that IGT is a better marker of prediabetes than IFG for diagnostic purposes; however, the consensus definition of MetS uses a fasting glucose cutoff of > 100 mg/dL, which has much lower sensitivity compared to postprandial glucose > 140 mg/dL (2 hours after 75 g glucose load) due to the ease of diagnosis and comparison.

Hyperinsulinemia and IR variably contribute to the other consequences that are subsumed under MetS: differential insulin sensitivity of tissues apparently contributes to atherogenic dyslipidemia, hypertension, nonalcoholic fatty liver disease, and PCOS. Multiple studies also implicate prothrombotic (increased levels of fibrinogen, plasminogen activation inhibitor–1, and other coagulation factors) and proinflammatory factors (raised hs-CRP, gamma glutamyl transferase, uric acid, elevated cytokines TNF-α and IL–6, and low adiponectin) in the etiology of acute coronary syndromes. Of these, the easiest to measure is hs-CRP, which has independent correlations with IR, adipose-derived cytokines IL–6 and TNF-α, as well as CVD: levels > 3.0 mg/dL should stimulate a search for other risk factors and evaluation for specific therapies, especially statins.

In summary, IR facilitates a clustering of abnormalities that contribute to CVD including prediabetes, hypertension, dyslipidemia, a procoagulant and proinflammatory state, endothelial dysfunction, and sympathetic overactivity. The above features have been shown to coexist (or cluster) in genetically predisposed individuals, especially as they gain weight and/or become sedentary. IR and BMI have good correlation, but studies demonstrate that whereas TG, HDL-C, glucose intolerance, and insulin levels expectedly correlate with high insulin levels are insulin sensitive, while one-fourth of IR individuals have insulin levels in the normal range. Studies suggest that IGT is a better marker of prediabetes than IFG for diagnostic purposes; however, the consensus definition of MetS uses a fasting glucose cutoff of > 100 mg/dL, which has much lower sensitivity compared to postprandial glucose > 140 mg/dL (2 hours after 75 g glucose load) due to the ease of diagnosis and comparison.

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1. **Atherogenic dyslipidemia:** This includes the quartet of elevated fasting TGs, low HDL-C, postprandial lipemia, and elevated small, dense LDL-C (sd-LDL) levels. The elevation of TGs with IR was noted over 50 years ago, and the mechanism appears to be differential insulin sensitivity: IR in skeletal muscles and adipose tissue promote higher insulin secretion (due to resistance to IMGU) and FFA concentrations (due to resistance to the antilipolytic function of insulin). This combination along with continued intake of refined carbohydrate rich diet stimulates VLDL-TG secretion by the insulin-sensitive liver, causing hypertriglyceridemia. A contrary view has also been proposed suggesting that the liver is also insulin resistant, creating a milieu where insulin is unable to inhibit hepatic VLDL-TG secretion; multiple lines of evidence make this unlikely. The most striking evidence comes from data showing much higher daylong insulin and TG levels in nondiabetic subjects consuming a 60% vs. 40% carbohydrate diet: a major benefit of reducing the total daily carbohydrate calories is a reduction in insulin and TG levels.

The higher the fasting TG levels, the higher the postprandial levels of other TG-rich lipoproteins (very low-density lipoprotein [VLDL], chylomicrons, and their remnants). However, postprandial lipemia is greater in IR individuals, even when they are matched for TG levels in insulin-sensitive subjects.

LDL particle size has been investigated but largely ignored in guidelines: individuals characterized as pattern B (smaller LDL particles < 255 Å) are apparently at higher risk of CVD compared to pattern A (larger LDL particles > 255 Å). Pattern B has been demonstrated to be closely linked to fasting TG levels over 150 mg/dL; furthermore, these individuals are also more likely to be IR, and have lower HDL-C levels. The major reason for restricting saturated fats (saturated fatty acids) has been the elevation of LDL-C levels: recent studies have established that sd-LDL is lowered by their consumption, while HDL-C is elevated. This may account for the neutral effects of saturated fatty acids on CVD or total mortality in various meta-analyses.

A low level of HDL-C is a well-established risk factor for CVD and frequently coexists with elevated TG levels. Evidently, the higher the VLDL secretion, the greater the transfer of cholesterol from HDL to VLDL (catalyzed by cholesterol ester transfer protein) in exchange for TGs, resulting in lower HDL-C levels. In addition, the fractional catabolic rate of apoprotein A–1 is increased by hyperinsulinemia in IR individuals, leading to a further reduction in HDL-C levels.

This pattern of high TG and low HDL-C levels with IR/hyperinsulinemia is so predictable that a TG/HDL-C ratio > 3 is the simplest surrogate marker of IR (r = 0.6), next only to plasma insulin response to a 75 g oral glucose load (r = 0.8), when compared to the IST.

2. **Hypertension:** Several studies demonstrate that nearly half of all hypertensive individuals are IR, and first-degree relatives of hypertensives, are more often IR than the normal population. Furthermore, IR is an independent predictor of hypertension on long-term follow-up, plasma insulin levels being an independent predictor of development of hypertension in both children and adults. Proposed mechanisms are considered to account for hypertension in IR subjects: increased sodium retention by the normally insulin sensitive kidneys, combined with an increased sympathetic drive by the autonomic nervous system (ANS). Hypertension is undoubtedly the most controversial component of
MetS, with at least half of all hypertensives having no evidence of IR.\textsuperscript{19,38} There are multiple population-based studies confirming and some refuting the association of hypertension with IR.\textsuperscript{51-53} The EGIR demonstrated that BP was directly related to plasma insulin levels and IR, but there was no evidence to suggest the converse (that IR may be secondary to hypertension).\textsuperscript{27,38} The main contention against this has been the failure to demonstrate hypertension to be related to IR by the technique of factor analysis (BP appears to correlate best with BMI in these studies, possibly due to enhanced RAS activity in obesity), a finding that is probably influenced by the fact that only half of hypertensive individuals are IR.\textsuperscript{19,20,21,36,38}

The major reason to look harder at this association is the weak benefit that good BP control offers in reducing CHD risk in comparison to stroke or heart failure.\textsuperscript{38} In this regard, another study by Reaven's group appears particularly instructive. They compared the plasma glucose and insulin responses to a 75 g oral glucose load in healthy volunteers, untreated patients with hypertension without CHD, and patients with hypertension and electrocardiographic evidence of CHD. The patients in the CHD group showed minor degrees of glucose intolerance but had significantly higher insulin and TG levels and lower HDL-C levels than the other 2 groups. Treating just the BP in these individuals did not return these metabolic abnormalities to normal values, however.\textsuperscript{54} Data from Copenhagen Male study also suggest that individuals with dyslipidemia had CHD independent of the baseline BP levels, while systolic and diastolic BP levels correlate with CVD risk only in individuals whose lipids were normal.\textsuperscript{55}

Thus, while the entire burden of essential hypertension cannot be explained by IR, the individuals who do have IR with hypertension are at greater risk of dyslipidemia, type 2 diabetes and CVD, and need more aggressive management of risk factors.

3. **Type 2 diabetes:** Himsworth first suggested that the large majority of diabetes is due to IR rather than insulin deficiency.\textsuperscript{56} Subsequently, multiple studies were performed to support this concept, as well as to conclude that first degree relatives of diabetics were relatively IR compared to those without such a family history. Furthermore, T2D developed only in individuals who could not sustain the hyperinsulinemia required to control blood sugar levels.\textsuperscript{1,17} There is also evidence cited above that obesity alone does not predict the development of diabetes if the individual is insulin sensitive, conveying that it develops only in those obese/nonobese individuals who are IR.\textsuperscript{17,26} Considering the fact that diabetes alone is a stronger risk factor for CVD than all the manifestations of MetS, IR should be of clinical relevance in the development and progression of CVD.\textsuperscript{11,18,43}

The above discussion highlights the multiple clinical and biochemical correlates of IR, and the wide variability in clinical picture of a proposed single entity. All the individual components of MetS have other causes apart from IR, but this typical clustering of risk factors (dyslipidemia, prediabetes, and hypertension) usually associated with excess adiposity occurs only in the setting of IR. Furthermore, it is individuals who are obese and IR, or hypertensive and IR, who are at the highest risk of diabetes and CVD.\textsuperscript{2,18,45}

**Is a Diagnosis of MetS or IRS Useful?**

MetS appears to be an attractive clinical diagnosis, signifying risk factor clustering with excess adiposity, inviting a full workup for other risk factors, lifestyle modification involving diet, exercise and weight loss, and drug therapy for specific conditions.\textsuperscript{7,4,12} However, there are few, if any, unique benefits of this diagnosis.

The underlying pathology of clinical MetS as defined by the consensus statement is not single (factor analysis studies).\textsuperscript{20,21} The attributable risk of MetS does not cover the entire spectrum of risk factors: FRS is a better predictor of 10-year CVD risk, though MetS adds information about lifetime risk.\textsuperscript{4,20} Obesity, prediabetes, dyslipidemia, HT on their own invite a recommendation of lifestyle modification and/or drug therapy, wherever appropriate.\textsuperscript{18,20} There is no common drug available that improves MetS or all its components. Hence, it appears futile to diagnose MetS as it is currently defined, and the best option appears to be to follow AHA's advice to evaluate and treat individuals with any one or more risk factors as per guidelines.

On the other hand, IRS is a totally different concept. Not only does IR explain the wide variability in insulin levels in population, it accounts in large part for the clustering of risk factors that is increasingly seen in urban populations. It has strong correlation with T2D and dyslipidemia, and a lesser but convincing association with hypertension as well.\textsuperscript{2,18,19,38,43} Together, this constellation of risk factors accounts for the rising burden of CVD, especially in females.\textsuperscript{34}

The last decade has seen the focus of primary prevention of CVD shift toward lipids, especially LDL-C, with increasing emphasis on statin use as the most important step. Statins, especially rosuvastatin, are known to increase the likelihood of developing diabetes (especially in women who are at much lesser risk of CVD in the first place), a finding that should evoke concern, knowing that diabetes is one of the most important risk factors for CVD.\textsuperscript{11,45} The weaker, still muddled concept of MetS has led to a dilution of IRS as a metabolic
risk factor with direct metabolic and vascular effects and a strong association with CVD, which definitely needs greater attention in view of the above discussion.14,18-20

Future Directions

The utility of further investigation can only lie in increased clarity about IR, its associated biochemical changes, and clinical syndromes. There is no other condition in which so many risk factors cluster together in a single individual, raising the risk for diabetes or CVD. Some of the possible lines for further investigation may include the following:

1. A clear definition of IRS: This can be done using simple clinical and biochemical parameters. At the core of the concept lie the following: resistance to IMGU/secondary hyperinsulinemia, which cause atherogenic dyslipidemia and endothelial dysfunction, conditions which are exacerbated by excess adiposity and physical inactivity in a genetically predisposed individual, especially with increasing age. A clinically applicable definition of IR will help in selecting subjects who are at higher risk among those presenting with isolated obesity, hypertension, or even for a routine health check-up: such individuals can be candidates for more aggressive risk management.

2. Investigating the prevalence of IR: This can be done in healthy individuals in population to establish the causes of metabolic abnormalities that cluster together. More investigation is needed to clarify the role of IR in hypertension.

3. Specific drugs that improve insulin sensitivity may be developed, and importantly, evaluated in large-scale trials: 2 new groups of antidiabetic drugs (SGLT2 inhibitors57 and GLP1-RA58) have shown promising results in reducing CV endpoints, including mortality, and could be evaluated in IRS as they are associated with weight loss in association with mild reduction of blood sugars and other hemodynamic and biochemical benefits. The increased risk of developing diabetes in subjects on high dose statins (especially rosuvastatin) also needs further evaluation, especially in view of its role in primary prevention of CVD, a subgroup which is not as high risk as those with established CVD.

4. The role of dietary patterns. Studying the role of dietary patterns in promoting or mitigating hyperinsulinemia or IR merits further study.

Conclusions

IR is a complex entity with many associated biochemical and clinical consequences, especially diabetes, hypertension, and CVD. MetS as currently defined is a weak concept and does not add information over and above that available with risk scoring systems like FRS. Efforts need to be made for a clear and clinically applicable definition of IRS, which will be both more applicable for routine screening and for the development of specific drug therapy.

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