



Commentary

Mediators of insulin resistance & cardiometabolic risk: Newer insights

Cardiometabolic risk refers to an increased susceptibility to cardiovascular diseases (CVDs) (stroke, myocardial infarction and peripheral artery disease) and metabolic disorders such as type 2 diabetes. Cardiometabolic risk factors include insulin resistance (IR), obesity, elevation in blood glucose, blood pressure, triglycerides and low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), smoking and inflammatory markers. While IR and obesity have been independently associated with cardiometabolic risk, IR has also been reported to be a critical mediator in the association between obesity and its comorbidities such as type 2 diabetes, hypertension and CVDs. IR has also been used in CV risk prediction models¹.

The development and progression of CVD can be assessed by measuring the baroreceptor sensitivity (BRS) index. Studies have shown a reduction in BRS in individuals with metabolic syndrome and IR^{2,3}, but the degree of BRS in IR and non-IR pre-obese and obese individuals has not been estimated so far. In this context, the study by Indumathy *et al*⁴ in this issue gains significance. Moreover, this study has evaluated the link of IR with BRS and cardiometabolic risk in normoglycaemic, normotensive pre-obese and obese adult Indian population. Indians are known to have the 'Asian phenotype' or 'South Asian phenotype' characterized by greater IR, higher abdominal fat, lower beta cell reserve and increased susceptibility to type 2 diabetes and CVD in spite of lower body mass index. A recent study tested the uniqueness of South Asian phenotype by comparing the cardiometabolic profile in resident South Asians with four different ethnic groups in the United States (US) and found that 8-15 per cent of men and 1-2 per cent of women of diverse ethnic backgrounds in US exhibited cardiometabolic profile similar to the South Asian phenotype⁵. This shows that the high-risk cardiometabolic profile is seen in other ethnic groups also, albeit at a lower prevalence.

In the study by Indumathy *et al*⁴, there was a significant reduction in BRS in the IR group as compared to non-IR group both in the pre-obese and obese categories. When the BRS index was compared between IR pre-obese and IR obese groups, there was no significant difference. This suggests that IR predisposes to CV risk, irrespective of the adiposity status. In fact, IR seems to set in at an earlier age in Asian Indians, and indeed the presence of hyperinsulinaemia has been demonstrated even in the cord blood⁶⁻⁸.

There are several evidences to suggest that the CV risk associated with IR could be contributed by dyslipidaemia. In the Framingham Heart Study, incident coronary heart disease risk associated with low HDL-C and high triglycerides was significantly increased only in the presence of IR in subjects without type 2 diabetes⁹. Similar findings have been reported in the normoglycaemic IR individuals studied by Indumathy *et al*⁴. They reported a significantly higher cholesterol, triglycerides and LDL-C and lower HDL-C levels in IR as compared to non-IR individuals both in the pre-obese and obese groups.

Inflammation is also an integral part of obesity and IR. Many inflammatory cytokines and adipokines such as tumour necrosis factor- α (TNF- α), interleukin (IL)-1, IL-6, IL-8, IL-10, plasminogen activator inhibitor 1, monocyte chemoattractant protein-1 (MCP-1), retinol binding protein-4, adiponectin, leptin, resistin, visfatin and chemerin, have been shown to be involved in the regulation of IR. The role of TNF- α , IL-6 and adiponectin in IR and obesity has been investigated by many researchers. In the case of abdominal obesity caused by excess visceral adipose tissue, increased amounts of inflammatory cytokines such as TNF- α , IL-6 and chemokines such as MCP-1 are secreted. TNF- α causes IR by inducing serine phosphorylation of insulin receptor substrate 1 (IRS1) and suppression of insulin signal transduction¹⁰. IL-6 induces IR by

reducing the expression of glucose transporter type 4 (GLUT4) and IRS1 by activating the JAK-STAT signaling pathway and increasing suppressor of cytokine signaling 3 (SOCS3) expression¹⁰. Increases in TNF- α and IL-6 induce the production of C-reactive protein (CRP) by the liver. CRP is the commonly used marker to assess systemic inflammation and is considered an inflammatory marker related to CVD¹¹. In line with the existing knowledge on the role of these inflammatory markers in IR and CVD, TNF- α , IL-6 and CRP levels were higher in IR individuals as compared to non-IR individuals in this study⁴, demonstrating the role of inflammation in IR and increased CV risk.

Adiponectin is a true adipokine which is exclusively produced by the adipose tissue. Binding of adiponectin to its receptors AdipoR1 and AdipoR2 results in activation of adenosine monophosphate-dependent kinase, PPAR- α (peroxisome proliferator-activated receptor-alpha) and other signalling pathways, eventually leading to insulin sensitization. Lower adiponectin levels have been associated with obesity and IR, both of which are the risk factors for cardiometabolic diseases¹². The hypoadiponectinaemia reported in the individuals with IR in this study⁴ could also contribute to the increased CV risk in these individuals.

Based on all the above observations, the proposed conclusions of this study⁴ are that:

- (i) Pro-inflammatory state, dyslipidaemia and hypoadiponectinaemia might contribute to cardiometabolic risk in IR individuals.
- (ii) The cardiometabolic risk observed in IR individuals is independent of the adiposity status.
- (iii) IR which occurs earlier than other metabolic abnormalities could be used for identifying individuals at increased risk for cardiometabolic diseases.

Although the study needs replication in larger samples before these findings are confirmed, one intriguing question mentioned by the authors themselves is whether the risk observed in these patients could be individual specific⁴. To investigate this, genetic studies and studies of gut microbiota might be the next logical steps. The role of genetic factors in increasing coronary heart disease risk has been shown in the studies on first-degree relatives, twin pairs, parents and offspring, and similarity of offspring to their biological compared to adoptive parents with heritable estimates of around 0.4-0.6¹³. One of the earliest genome-wide association studies (GWASs) showed that the SNP rs1333049

near *CDKN2A* and *CDKN2B* on chromosome 9 was significantly associated with susceptibility to coronary heart disease¹⁴. The same locus was also associated with type 2 diabetes in subsequent studies¹⁵. Recently, a multi-trait GWAS has identified 53 loci which include 43 new loci for IR¹⁶. A genetic profiling of study subjects might give an idea about the cardiometabolic risk carried by these individuals based on number of risk variants carried by them.

The human gut microbiota has been intensively studied in the past few years, and dysbiosis, a change in the composition and function of gut microbiota, has been found to be associated with the pathogenesis of cardiometabolic disorders¹⁷. A change in gut microbiota profile has also been shown to be associated with increased CV risk in a study on patients with highest and lowest lifetime burdens of CVD risk factors¹⁸. In patients with symptomatic atherosclerosis, *Collinsella* has been found to be increased and a lower ratio of *Bacteroidetes* to *Firmicutes* has been associated with obesity. Changes in the amount of *Bifidobacterium*, *Lactobacillus* and *Clostridium* as well as a reduced *Firmicutes* to *Bacteroidetes* ratio have been reported in type 2 diabetes¹⁹. In addition, a reduction in the number of Clostridiales bacteria (*Roseburia* species and *Faecalibacterium prausnitzii*), which produce short-chain fatty acid (SCFA) such as butyrate, has also been reported^{19,20}. Studies have also shown that gut microbial dysbiosis results in increased gut permeability causing absorption of macromolecules from the intestinal content. This triggers systemic immune alterations, altered signalling pathways affecting lipid and glucose metabolism and low-grade inflammation, eventually leading to IR and type 2 diabetes²¹.

Studies have also shown the role of gut microbiota-derived molecules in cardiometabolic disorders. SCFAs from gut microbiota affect insulin sensitivity, while administration of SCFAs without changing food intake or exercise increased insulin sensitivity in mice fed on a high-fat diet²². It has also been shown that intestinal microbial metabolism contributes to the generation of uraemic retention molecules such as trimethylamine-N-oxide (TMAO)²³, which has been implicated in atherosclerosis, platelet aggregation, diabetes, hypertension and chronic kidney disease. Strategies such as administration of TMAO inhibitors, faecal microbiota transplantation and use of prebiotics and probiotics to restore the balance in the microbiome, are being tried in the prevention/treatment of CVD.

More studies on the 'Asian Indian phenotype' are needed as this can help us to understand more completely the pathogenesis of IR, the type 2 diabetes and CVD.

Conflicts of Interest: None.

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