# Targeting Abdominal Obesity in Diabetology

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The hallmarks of diabetes are obesity and weight gain, mainly involving abdominal fat, and approaches to addressing these were discussed by Luc Van Gaal, MD, PhD, Antwerp University Hospital, Antwerp, Belgium. Persons with type 2 diabetes mellitus (T2DM), especially the obese, tend to have more visceral fat than persons with type 1 [Gallagher D et al. *Am J Clin Nutr* 2009]. Conventional treatments of diabetes typically produce weight gain over time involving subcutaneous and visceral fat [UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; Kahn SE et al. *N Engl J Med* 2006].

Therapeutic weight control studies in patients with T2DM have assessed sulfonylurea, thiazolidinediones, insulin, metformin, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists. Weight loss has been documented only for metformin (50% of cases) and GLP-1 receptor agonists [Drucker DJ. *J Clin Invest* 2007].

Diet and aerobic exercise are beneficial in reducing visceral fat [Després JP et al. *Am J Physiol* 1991; Ross R et al. *Ann Intern Med* 2000; Christiansen T et al. *Eur J Endocrinol* 2009]. Resistance exercise also reduces visceral fat and intrahepatic lipids [Lee S et al. *Diabetes* 2012]. Aerobic and resistance exercise also reduces body weight and waist circumference in older individuals [Davidson LE et al. *Arch Intern Med* 2009]. Even without weight loss, exercise increases skeletal muscle mass, cardiorespiratory fitness, and insulin sensitivity [Ross R, Bradshaw AJ. *Nat Rev Endocrinol* 2009].

Oral drug therapy for weight and abdominal fat control in diabetes includes topiramate plus phentermine, and lipase inhibition (orlistat). Despite the weight lowering effects of sibutramine [Van Gaal LF et al. *Int J Obes Relat Metab Disord* 1998], concerns about the increased risk of adverse cardiovascular (CV) events [James WP et al. *N Engl J Med* 2010] have prevented approval in some countries.

Second-generation peripheral CB1 antagonists, 11β hydroxysteroid dehydrogenase inhibitor, growth hormone in lipodystrophy, GLP-1 analogues (liraglutide, exenatide), SGLT-2 inhibitors (dapagliflozin), and leptin plus pramlintide are novel medications being studied to reduce intra-abdominal fat.

Official Peer-Reviewed Highlights From the 4th International Congress on Abdominal Obesity

International Chair on Cardiometabolic Risk

## TARGETING LDL-C

Kwang Kon Koh, MD, PhD, Gachon University Gil Medical Center, Incheon, South Korea, discussed targeting low-density lipoprotein cholesterol (LDL-C) in patients with abdominal obesity.

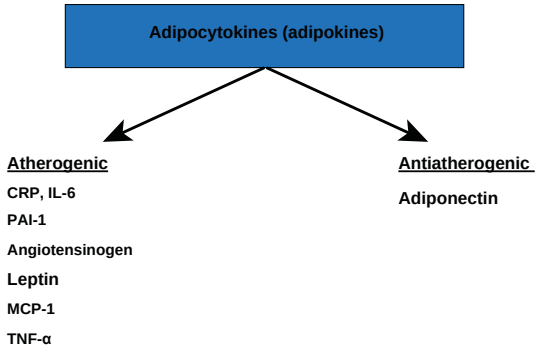
Patients with hypertension and diabetes are at increased risk of CV events. Long-term survival is also significantly decreased compared to patients without diabetes [Verdecchia P et al. *Hypertension* 2004]. Thus preventing the development of diabetes is an important treatment goal.

Visceral fat is a hallmark of obesity and may drive inflammation and insulin resistance. In turn, this increases the risk of hypertension, T2DM, and dyslipidemia. These important risk factors increase the risk of developing atherosclerosis and cardiovascular disease (CVD) [Lim S et al. *Circ J* 2011; Koh KK et al. *Int J Cardiol* 2012].

Adipocytes produce bioactive molecules that participate in diverse metabolic processes [Lau DC et al. *Am J Physiol Heart Circ Physiol* 2005; Wellen KE, Hotamisligil GS. *J Clin Invest* 2005] (Figure 1). With increasing visceral adipose mass, adiponectin secretion decreases and the secretion of adipokines that reduce insulin sensitivity and contribute to endothelial dysfunction is increased. Thus, obesity and T2DM heighten CV risk.

Simvastatin lowers adiponectin and reduces insulin sensitivity in patients with hypercholesterolemia [Koh KK et al. *Diabetes Care* 2008], while atorvastatin and rosuvastatin increase glucose and insulin sensitivity in such patients [Koh KK et al. *J Am Coll Cardiol* 2010; Koh KK et al. *Int J Cardiol* 2013]. Atorvastatin and rosuvastatin mildly increase the risk of diabetes [Sattar N et al. *Lancet* 2010; Goldstein MR, Mascitelli L. *Curr Diab Rep* 2013].

Figure 1. Adipose Tissue as an Endrocrine Organ




CRP=C-reactive protein; IL-6=interleukin-6; MCP-1=monocyte chemoattractant protein-1; PAI-1=plasminogen activator inhibitor-1; TNF-α=tumor necrosis factor-alpha

However, insulin resistance and endothelial dysfunction are both subject to multiple influences. Interactions between insulin resistance and endothelial function may mediate the pathophysiology of conditions such as diabetes, obesity, dyslipidemia, coronary artery disease, hypertension, and atherosclerosis [Mora S et al. *Circulation* 2012]. Combined statin-based therapy has shown promise in improving oxidative stress [Koh KK et al. *Circulation* 2004], altering levels of triglycerides and high-density lipoprotein cholesterol, and increasing insulin sensitivity [Koh KK et al. *Hypertension* 2005; Koh KK et al. *J Am Coll Cardiol* 2005].

Thus, despite the concerns about an increase risk of diabetes with use of potent statins, they have a central role in the primary and secondary prevention of coronary heart disease (CHD), in concert with modifiable lifestyle changes, stated Prof. Koh (Table 1).

Table 1. Practical Recommendations for Statin Choice

| Primary Prevention | Secondary Prevention |
|---|---|
| Without risk factors* for diabetes: low (for Asian) or optimal (for Caucasian) dose statins alone; statins with beneficial metabolic actions such as pravastatin | In acute coronary syndrome state: potent, high dose statins because cardiovascular benefits of statins exceed diabetogenic or other risks |
| With risk factors for diabetes: low or optimal dose statins combined with RAAS blockades, PPAR agonists, ezetimibe or metformin to reduce diabetogenic effect of statins | In stable coronary artery diseases: optimal dose statins combined with RAAS blockades, PPAR agonists or ezetimibe |

+Individuals should lose weight and take regular physical exercise.

*Impaired fasting glucose or impaired glucose tolerance, family history of diabetes.

## HYPERTRIGLYCERIDEMIC WAIST AND CARDIOMETABOLIC RISK

Benoit Arsenault, PhD, Université Laval, Québec City, Québec, Canada, discussed waist circumference and the risk of CVD.

Myocardial infarction risk increases with increasing body mass index (BMI) and waist circumference [Yusuf S et al. *Lancet* 2005]. Visceral, but not subcutaneous adiposity, is associated with adverse CV events [Britton KA et al. *J Am Coll Cardiol* 2013].

Studies have indicated the importance of the hypertriglyceridemic (HyperTG) waist phenotype – the combination of increased waist circumference and elevated triglycerides – for prediction of cardiometabolic risk and associated CVD risk. The relationship between visceral fat and increased coronary artery calcium score in HyperTG waist patients with T2DM has been described [Sam S et al. *Diabetes Care* 2009], as has the increased risk of coronary heart disease [Arsenault BJ et al. *Can Med Assoc J* 2010]. In the latter study, the HyperTG waist phenotype was associated with the most precipitous decline in probability of event-free survival.

The collective findings have led to a number of conclusions and recommendations (Table 2).

Table 2. Important Aspects of the HyperTG Waist

| |
|---|
| The HyperTG waist is the most simple, optimal, and inexpensive way of assessing the high-risk obesity phenotype at the population level |
| HyperTG waist is associated with an altered cardiometabolic risk profile, and important predictor of incident CVD and T2DM, and may be useful in risk stratification |
| Clinical cutpoints for waist circumference and triglyceride levels need to be established for other ethnic groups |
| The HyperTG waist should be used together with CVD risk prediction algorithms to provide a better assessment of CV risk |
| Additional studies are required to determine whether or not HyperTG waist could be used to monitor the efficacy of lifestyle modification therapy at the population level |

## GLOBAL CARDIOMETABOLIC APPROACH ORGANIZATION AS A MODEL

Denis Richard, PhD, Université Laval, Québec City, Québec, Canada, reviewed the Canadian network for research in cardiometabolic health, diabetes, and obesity (CMDO).

The prevalence of obesity in Canada has increased from almost 15% in 1979 to nearly 25% in 2008. Canada ranks among the top nations globally in terms of national prevalence of diabetes, which, for Canadians aged 35 to 39 years and 40 to 44 years has increased from 1.5% and 2% respectively in 1998, to 2.5% and 4% respectively in 2008. Thirty three percent of Canadians die of diabetes-related causes annually.

The CMDO network comprises research silos of cardiometabolic health, diabetes, and obesity. The CMDO network emphasizes basic and preclinical research, nutrition, physical activity, human physiopathology, lifestyle habits, population health, health care delivery and policy and knowledge dissemination/exchange.

As CMDO strives to move away from a silo-based approach, long-term collaborative research will be needed to study the association of cardiometabolic health, diabetes, and obesity with respiratory diseases and cancer [Boulet LP. *Clin Exp Allergy* 2013] [Gilbert CA, Slingerland JM. *Ann Rev Med* 2013].