Central obesity and the cardiometabolic syndrome in Hispanics

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Obesity continues to increase dramatically in both industrialized and nonindustrialized countries. The scope of the problem in Hispanic populations follows a similar epidemic pattern to industrialized countries, but the unfavorable social and economic features of these populations have placed them at increased risk of developing cardiometabolic syndrome and cardiovascular disease. Some pathophysiologic elements of obesity appear to have a differential biologic behavior in these populations, suggesting that not only environmental factors, but also genetically determined conditions, can influence obesity-related cardiometabolic risk. However, the high epidemiologic diversity of these populations and the lack of reliable statistics make it difficult to ascertain the characteristics of obesity in Hispanics, especially as most of the available data come from Hispanics living in industrialized countries. The management of obesity in Hispanic populations is similar to that in non-Hispanics, and is based on lifestyle changes, weight-reducing medication and bariatric surgery. Novel research related to gut-derived hormones and the endocannabinoid network will potentially contribute to treat obesity better. Newer studies taking into account ethnic differences will result in improved therapeutic alternatives for the prevention of obesity and cardiometabolic syndrome-related cardiovascular disease if they can be coupled with improved living conditions.

Keywords: adiponectin, cardiometabolic risk factors, central obesity, endocannabinoid receptors, gut-derived hormones, hispanic diversity

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Expanding scope of the problem

The facts are undisputable: obesity is the fastest growing disease in both industrialized and non-industrialized countries. In the USA, the prevalence of this condition has increased by 110% since the 1970s [1]. It is also calculated that more than 65% of the total population is overweight or obese, and that excess-associated metabolic complications affect more than half of all adults in the USA [2]. Overweight is defined by the WHO as a BMI of 25–29.9, while obesity is defined as a BMI above 30. The definition of obesity must, however, consider other anthropometric measurements, such as waist circumference (WC), waist-to-hip ratio (WHR) and, as will be discussed below, the ethnicity of the patients.

On the other hand, the clustering of cardiovascular disease (CVD) and metabolic risk factors, which include abdominal/visceral obesity, dysglycemia, hypertension, dyslipidemia and recently microalbuminuria has been well established for a long time, and collectively constitutes the cardiometabolic syndrome (CMS) [3]. Numerous national and international expert groups, which include the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP)III, the European Group for Study of Insulin Resistance (EGIR), the American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) have developed specific definition criteria, which collectively acknowledge the growing importance of the CMS and its diagnosis. The different definition systems available may differ in the use of insulin resistance indices, glycemic and blood pressure thresholds, the clinical measurement of abdominal adiposity and the presence of microalbuminuria. However, they all have something in common: they all require the presence of obesity (**Box 1**).

Obesity is widely considered to be the driving force behind the increase in the prevalence of CMS in US adults, which could exceed 34% (by IDF criteria) according to recent analysis from the third National Health and Nutrition Examination Survey (NHANES III) [4]. Importantly, obesity in children and adolescent populations is dramatically increasing and has also been linked to a higher prevalence of the CMS, according to the NHANES III survey [5].

In both adult and pediatric populations, minorities appear to be at increased risk of excess adiposity and secondary comorbidities. Indeed, it has been demonstrated that Hispanic and non-Hispanic African–Americans are at a higher risk [6]. The NCEP-ATP III has acknowledged these considerations, and has tracked the causes of the CMS to genetic/ethnic factors and physical inactivity [6].

10.2217/14750708.4.5.609 © 2007 Future Medicine Ltd ISSN 1475-0708

Box 1. Classification criteria for the cardiometabolic syndrome.

WHO 1998

- Disglycemia: fasting glycemia ≥110 mg/dl or impaired glucose tolerance (>140 mg/dl or insulin resistance)

AND two or more of the following:

- Dyslipidemia: TG ≥150 mg/dl and/or HDL <35 mg/dl (men), <40 mg/dl (women)
- BP >140/90
- Microalbuminuria >20 µg/min

European Group for the Study of Insulin Resistance (1999)

Insulin resistance: hyperinsulinemia >25%
AND two or more of the following:

- Central obesity: WC ≥94 cm (men), ≥80 cm (women)
- Dyslipidemia: TG >170 mg/dl or HDL <40 mg/dl
- Hypertension: BP ≥140/90 and/or on medication
- Dysglycemia ≥110 mg/dl

Adult Treatment Panel III (2001)

Three or more of the following:

- Central obesity: WC ≥102 cm (men), ≥88 cm (women)
- Dyslipidemia: TG ≥150 mg/dl; HDL <40 mg/dl (men), <50 mg/dl (women)
- Hypertension: BP ≥135/85, or on medication
- Fasting glucose >110 mg/dl

International Diabetes Federation (2005)

- Central obesity: WC ≥94 cm (men), ≥80 cm (women, euripoids); Hispanics: 90 cm (men), 80 cm (women)

AND two or more of the following:

- Disglycemia: fasting glycemia ≥100 mg/dl
- Dyslipidemia: TG ≥150 mg/dl, or on medication
- HDL <40 mg/dl (men), <50 mg/dl (women), or on medication
- Hypertension: SBP ≥130 or DBP ≥85 mmHg, or on medication

American Association of Clinical Endocrinologists (2003)

Risk factors:

- Overweight: BMI >25 or a WC of >40 inches (men), >35 inches (women) (10–15% lower for non-Caucasians)
- Sedentary lifestyle
- Age >40 years
- Non-Caucasian ethnicity
- Family history of Type 2 diabetes, hypertension or cardiovascular disease History of glucose intolerance or gestational diabetes
- Acanthosis nigricans
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease

Characteristic abnormalities of insulin resistance syndrome:

- Dyslipidemia: TG ≥150 mg/dl, HDL <40 mg/dl (men), <50 mg/dl (women)
- Hypertension: BP ≥135/85, or on medication
- Fasting glucose >110 (100) mg/dl

Diagnosis is made by the presence of one risk factor AND two or more characteristic abnormalities

BP: Blood pressure; DBP: Diastolic blood pressure; HDL: High-density lipoprotein; SBP: Systolic blood pressure; TC: Total cholestrol; TG: Triglyceride; WC: Waist circumference.

The heterogeneous Hispanic population: is there a 'Hispanic Paradox'?

Hispanic, or Latino, is a term commonly used to describe populations of Spanish heritage and culture, including South American, Central American, Cuban, Mexican and Puerto Rican populations. The Hispanic population is rapidly growing and it is estimated that it will attain approximately a quarter of the US population by the year 2050, according to the US Census Bureau in 2005 [101]. In addition, the Hispanic population is quite heterogeneous in terms of social economic, cultural, nutritional and healthcare coverage status. As an example, it has been documented by Frisbie *et al.* that Puerto Ricans living in the USA have higher infant mortality rates when compared with Mexicans and Cubans [7].

In addition, some epidemiologic studies report that Hispanics residing in the US have similar or improved health conditions compared with the non-Hispanic white population, despite unfavorable incomes and education status, as well as relative lower mortality rates. This unexpected finding has been termed as the 'Hispanic Paradox' [8]. This phenomenon would favor, in particular, male and elderly populations as well as those originally born in Mexico [8]. These findings have been at least partially attributed to specific cultural factors present in the Hispanic population that could counterbalance the influence of poverty and associated deficiencies in healthcare on mortality and morbidity [9]. Some of the factors hypothesized to account for this apparent beneficial influence include differences in dietary patterns [10], tobacco abuse, alcohol use, BMIs and levels of physical activity [9].

However, recent studies challenge the existence of the 'Hispanic Paradox'. Analysis of 1438 Mexican–American adults included in the San Antonio Heart Study followed-up during an average period of 14.5 years found a similar risk of mortality for all-cause, cardiovascular and coronary heart disease (CHD) in nondiabetics, as well as in diabetics treated with insulin compared with non-Hispanic whites [11]. Moreover, in this study the risk of mortality was significantly higher in the Hispanic diabetic group not treated with insulin. In addition, Crimmins *et al.* analyzed a cohort of the NHANES survey from 1999–2002, which studied 4206 adult participants (aged >40 years), and compared CVD risk factors including blood pressure,

BMI, lipid profile, glycohemoglobin, C-reactive protein (CRP), fibrinogen and albumin for white, black and Hispanic subjects [12]. Interestingly, in this study the heterogeneity of the Hispanic population was accounted for, and participants were stratified into US-born Hispanics, foreign-born Hispanics and Hispanics of specific Mexican origin. Hispanics had higher cardiovascular risk compared with the white group, but lower than African–Americans. After controlling for socioeconomic status, the differences between whites and Hispanics disappeared. However, after adjustments for place of birth, foreign-born Hispanics and non-Hispanic whites had lower risk compared with US-born Mexicans. According to the authors, these findings argue against the existence of a 'Hispanic Paradox' in terms of risk profile and the apparent differences previously found are more related to biases imposed by the high heterogeneity of the Hispanic population, are reflected in socioeconomic status differences, which in turn result in differential access to healthcare. Interestingly, the better profile in foreign-born Hispanics could be attributed to immigration of healthy individuals to the USA, with out-migration of the diseased to their countries of origin, which is known as migrant health selectivity.

Interestingly, other paradoxical findings reflecting the heterogeneity of the Hispanic population, this time living in Latin America, has been reported. In some Latin American countries with emerging economies, such as Brazil, the simultaneous occurrence of underweight in children and overweight/obesity in adults coexisting in the same family is an emerging phenomenon [13]. This appears to affect approximately up to 60% of households in which an underweight individual lives [14]. This double burden appears to be linked to easy access to fast, cheap and energy-dense foods, which lead to increased caloric intake, as opposed to poorer countries, affected by scarcity of food [13]. This, as well as certain social inequities characteristic in Latin American countries, has resulted in the paradoxical situation of simultaneously increased rates of both undernutrition and obesity similar to those of industrialized countries [15].

Further studies addressing these differences will be particularly useful to identify populations at increased risk CVD, in which efforts directed at prevention and treatment should be initiated or intensified.

Central obesity & distribution of adiposity: evolving concepts

As previously discussed, obesity largely drives the dramatic increase in the incidence and prevalence of the CMS worldwide [3]. Ethnicity is taken into account in the newer IDF definition criteria, according to which, the WC cut-off in Hispanic men is 90 cm and 80 cm in women, resulting in a significantly higher prevalence of CMS in Mexican-Americans (50.6%), compared with non-Hispanic white subjects [4].

Genetic factors certainly influence excess adiposity, but environmental factors, in particular diet and exercise patterns, account for most excess adiposity. Indeed, industrialization of societies has resulted in a drastic reduction in the levels of physical activity, while simultaneously energy intake has increased, derived mainly from highly caloric fat-dense foods.

Distribution of adiposity in the CMS is also of importance. It has been demonstrated that visceral-type adipose tissue distribution is associated with the presence of CMS in both elderly men and women, even in the presence of normal body weight [16]. A study including 596 adult Hispanics (aged 60–92 years) of Caribbean origin (mainly Puerto Ricans and Dominicans) living in Massachusetts (USA) analyzed the association between BMI, WC and Type 2 Diabetes Mellitus (DM2), compared with 239 non-Hispanic whites [17]. Central obesity (WC >102 cm), was present in 42.3% of Puerto Ricans and 36.6% of Dominican men, similar to 46.4% of non-Hispanic men. Among women, central obesity (WC >88 cm) was detected in 74.3% of Puerto Ricans, 76.5% of Dominicans and 62.7% of non-Hispanic whites. No significant differences were reported. DM2 was more prevalent at all BMI and WC categories in the Hispanics, while DM2 was more prevalent (41 and 43%, respectively, for Puerto Rican and Dominicans) in participants with BMI of 25–29. By contrast, in whites, DM2 prevalence was highest in obese individuals (36–45%). Both BMI and WC were significantly correlated with DM2, but the association was stronger for non-Hispanic Whites. Overall, this study indicates a differential effect of regional adipose tissue deposition (total vs central adiposity) between Hispanics and non-Hispanic whites, requiring further studies in order to elucidate this relationship.

Another study derived from the NHANES III also illustrates the role of ethnic differences related to abdominal obesity in diabetics [18]. In this paper, Okosum and colleagues reported

significantly lower rates of diabetes awareness in centrally obese (as measured by WC) Hispanic patients compared with non-Hispanic Whites, both in adult men and women (21 vs 74% in men; 23 vs 77% in women), as well as lower rates of treatment (14 vs 70% in men; 23 vs 57% in women). Obese patients also had worse glycemic control (glycohemoglobin <8%) (30 vs 64% in men; 19 vs 77% in women), and individuals with central obesity had poorer glycemia control when compared with nonobese subjects.

It is generally accepted that visceral adipose tissue in overweight and obesity could serve as a source of increased fatty acid (FA) delivery to the portal circulation, leading to insulin resistance in the liver [19]. However, there is also evidence for insulin resistance mediated by both subcutaneous adiposity and total body fat [20]. Indeed, lipids abnormally deposited in tissues such as skeletal muscle and pancreatic β-cells can also induce insulin resistance and DM2 [21]. Some studies have linked triglyceride accumulation in skeletal muscle, in particular intramyocellular triglyceride content, and insulin resistance *in vivo* [22]. Finally, it is well established that abnormalities in the development of adipose tissue lead to ectopic lipid deposits in the liver and skeletal muscle and are related to severe insulin resistance.

Metabolic abnormalities in obesity: adipokines

Adipose tissue in obese individuals is dysfunctional, both from functional and morphologic standpoints. Adipocyte differentiation from mesenchymal pluripotential stem cells involves numerous transcriptional and post-transcriptional events. Disturbances in one or more of these differentiation and proliferation steps could lead to failure of adipose tissue in adaptation to excess caloric intake, dysfunctional adipose tissue characterized by enlarged adipocytes, ectopic lipid deposits and insulin resistance [21].

On the other hand, adipose tissue is a complex endocrine organ and numerous substances with both endocrine and paracrine activity are produced by fat tissue cells. Most currently identified adipokines – with the exception of adiponectin – exert a proinflammatory activity, as is depicted in **Box 2**. Substances such as FAs are released from adipocytes and are strongly implicated as a cause of insulin resistance, a key component of the CMS, as well as DM2 [15,16], as they interfere with intracellular insulin signaling [23,24]. In addition, adipokines influence the inflammatory, procoagulant, antifibrinolytic and vasoactive cascades (**Figure 1**).

Box 2. Proinflammatory and anti-inflammatory adipokines.

Proinflammatory adipokines

- Tumor necrosis factor-α
- Interleukin 1
- Interleukin 6
- Resistin
- Leptin
- Monocyte chemoattractant protein 1
- Angiotensin II
- Renin angiotensin aldosterone system
- Fibrinogen
- Plasminogen activator inhibitor 1

Anti-inflammatory adipokines

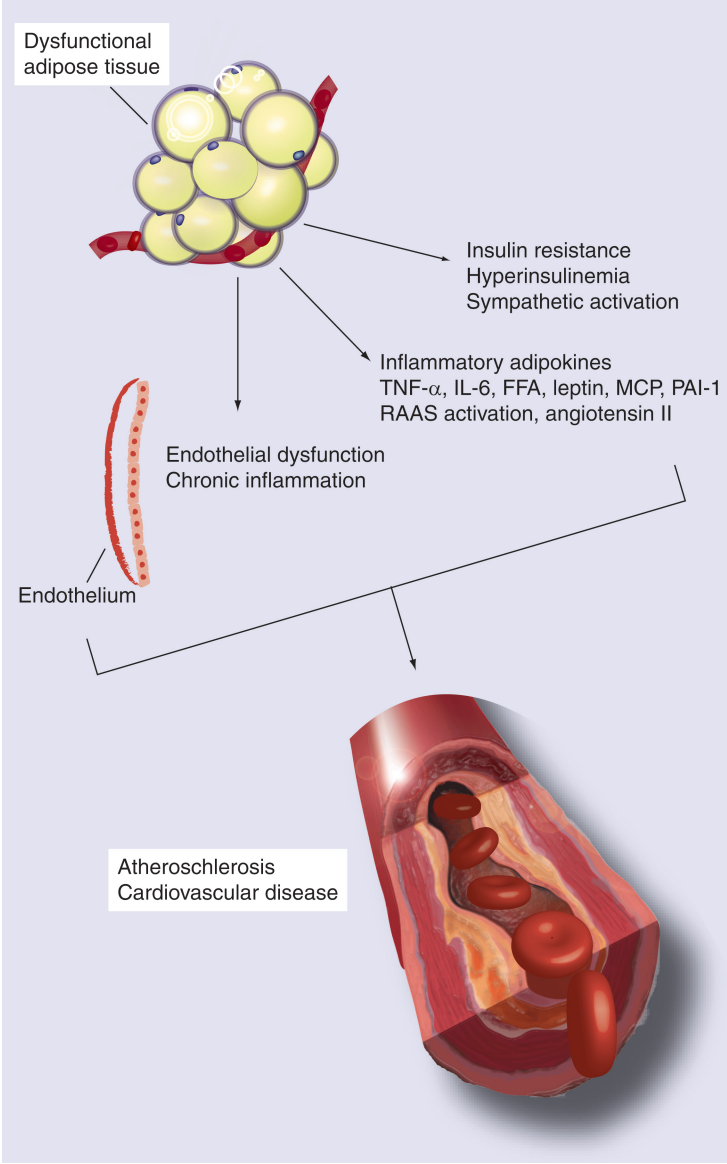
- Adiponectin

Adiponectin: an anti-inflammatory adipokyne with ethnic variability?

Since its characterization in 1995, this interesting adipokine has received many different names, such as adipoQ, AcrP30 and gelatin ligand protein. It is produced specifically in adipose tissue as a 30 kDa protein, and preserves great homology with collagen (type VIII and X) and with the C1q component of the complement system. Adiponectin levels are negatively related to insulin resistance, fat mass (in particular of visceral distribution), dyslipidemia and DM2.

Two main adiponectin isoforms are found in peripheral blood, the complete molecule (fAd) and a globular fraction (gAd), resulting from fAd cleavage. In addition, two types of adiponectin receptors have already been cloned, and have been characterized as seven transmembrane domain proteins not coupled to G-proteins [25]. Adiponectin receptor 1 (AdipoR1) has great affinity for gAd, and is expressed mainly in skeletal muscle. AdipoR2 is more abundant in liver and its affinity is intermediate for fAd and gAd [25]. The mechanisms of action of adiponectin have not been fully elucidated. Nonetheless, this adipokyne seems to induce a rise in FA oxidation in skeletal muscle, which are potent inductors of lipotoxicity [26]. Other potential mechanisms include reduction in hepatic glucose output, along with inhibition of adhesion molecule expression (intercellular adhesion molecule [ICAM]-1, vascular cell adhesion molecule [VCAM]-1, E-Selectin) and TNF-1α [26,27].

Figure 1. Cardiometabolic risk factors, adiposity and insulin resistance in the development of atherosclerosis.



FFA: Free fatty acid; MCP: Monocyte chemoattractant protein; PAI: Plasminogen activator inhibitor; RAAS: Renin-angiotensin-aldosterone system.

Some experimental trials have shown suppression of both macrophage migration and their transformation into foam cells, nitric oxide (NO) synthesis triggering, and reduction of vascular intimal proliferation [27]. *In vitro* and *in vivo* studies have reported a 30% reduction in atherogenesis attributable to adiponectin [25].

Adiponectin is able to stimulate the activity of AMP-activated protein kinase (AMPK), which triggers a series of catabolic reactions, such as FA oxidation, that have an insulin-sensitizing effect. TNF-1α activity is also blocked by this adipokine, resulting in blockade of phosphorylation and activation of the proinflammatory mediator nuclear factor αB. AMPK stimulation also induces NO synthesis, which that could explain its beneficial effects on endothelial function and anti-atherogenic activity. Finally, the gAD isoform inhibits cellular proliferation and reactive oxygen species, induced by oxidized low-density lipoprotein (LDL) during atherosclerotic plaque formation [28].

There is evidence in pediatric populations that adiponectin may be an important predictor of CMS [29] and that hypoadiponectinemia predicts insulin resistance and DM2 in adults [30]. Interestingly, low levels of this cytokine have been demonstrated in Hispanic children with DM2 compared with nondiabetics [31]. In addition, a recent study in 175 overweight Hispanic children (average age: 11.1 years) living in the USA with a family history of DM2 found that hypoadiponectinemia is an independent marker of the CMS [32]. Indeed, in this study there was a significant correlation between adiponectin and systolic blood pressure, WC, triglycerides, 2 h postchallenge postprandial glucose and high-density cholesterol (HDL). The relationship was independent of age, gender, body composition, insulin sensitivity and degree of sexual maturation (Tanner stage). Adiponectin levels were approximately 25% higher in 'healthy' overweight participants compared with those with CMS, and were independent of insulin sensitivity and central obesity.

Another recent study by Hanley *et al.* found ethnic differences in adiponectin related to the CMS [33]. A cross-sectional analysis derived from the Insulin Resistance and Atherosclerosis Family study (IRAS Family) looked at adiponectin in 1636 nondiabetic Hispanic and African–American participants, relative to indices of insulin sensitivity, lipid profile, CRP, visceral and subcutaneous adiposity. Adiponectin levels were positively correlated to age, gender (female), HDL, subcutaneous fat and insulin sensitivity, while CRP, visceral fat and glucose were negatively correlated to adiponectin. The association between adiponectin, insulin sensitivity and both visceral and subcutaneous-type adiposities was independent of the other components of the CMS. There was a significantly lower association between visceral adiposity and adiponectin in Hispanics compared with African–Americans, again suggesting ethnicity-related variation in the role of adiponectin in the development of the CMS.

Although much research is needed in this field, adiponectin emerges as an important adipokine, with great anti-inflammatory, insulin-sensitizing and endothelial modulation activities. Available studies suggest different patterns of adiponectin relationship to the CMS in Hispanics, which will need to be taken into account when designing therapeutic interventions directed at controlling the development of CMS in this population.

Therapy for obesity: emergent pharmacologic strategies targeted at the CMS

Treatment of obesity and its associated comorbidities, in particular CMS, DM2, certain forms of cancer and CVD, has proven to be more than challenging. It is generally accepted that weight loss through lifestyle interventions and pharmacotherapy attain between 5 and 10% – which can reach 15% in some cases – of weight reduction compared with the baseline. Unfortunately, most interventions do not induce long-term maintenance of the lost weight and patients typically regain their initial weight in the long term [34].

It is accepted that moderate reductions in weight, between 5 and 10%, significantly reduce the risk of obesity-related CVD [35]. For instance, in the Diabetes Prevention Program (DPP), a randomized, controlled trial in which 3234 nondiabetic adult individuals with dysglycemia where assigned to placebo, metformin or therapeutic lifestyle intervention, showed that weight loss between 5–10% among the obese patients – including 508 Hispanics living in the USA – resulted in a reduction in the incidence of DM2 of approximately 58% over a mean period of 2.8 years [36].

Bariatric surgery emerges as an important tool in current management of obesity, as available procedures result in weight loss that oscillates between 47.5% for gastric banding, to more than 70% in adult patients undergoing biliopancreatic diversion or duodenal switch. This form of treatment also appears to positively affect CVD risk factors, such as DM2, hyperlipidemia, hypertension and obstructive sleep apnea, according to a recent meta-analysis [37]. Furthermore, surgical management of obesity can result in cure of DM2 in some patients [38] and future studies are likely to study its effects on normal-weight and moderately overweight patients with DM2. The role of bariatric surgery in the treatment of obesity, CMS and CVD is indeed a field of active research, however it is beyond the scope of this review, which is focused on the pharmacotherapy aspects of obesity.

Numerous agents are currently available for management of obesity, which can be classified as appetite suppressants and lipase inhibitors, of which sibutramine and orlistat are the most commonly used and studied (**Table 1**). Overall, available literature supports a weight loss of approximately 4–5 kg at 12 months for sibutramine, and 2.89 kg for orlistat at 1 year [39]. However, long-term studies are still lacking and final conclusions regarding the sustainability of this weight loss cannot be made at present.

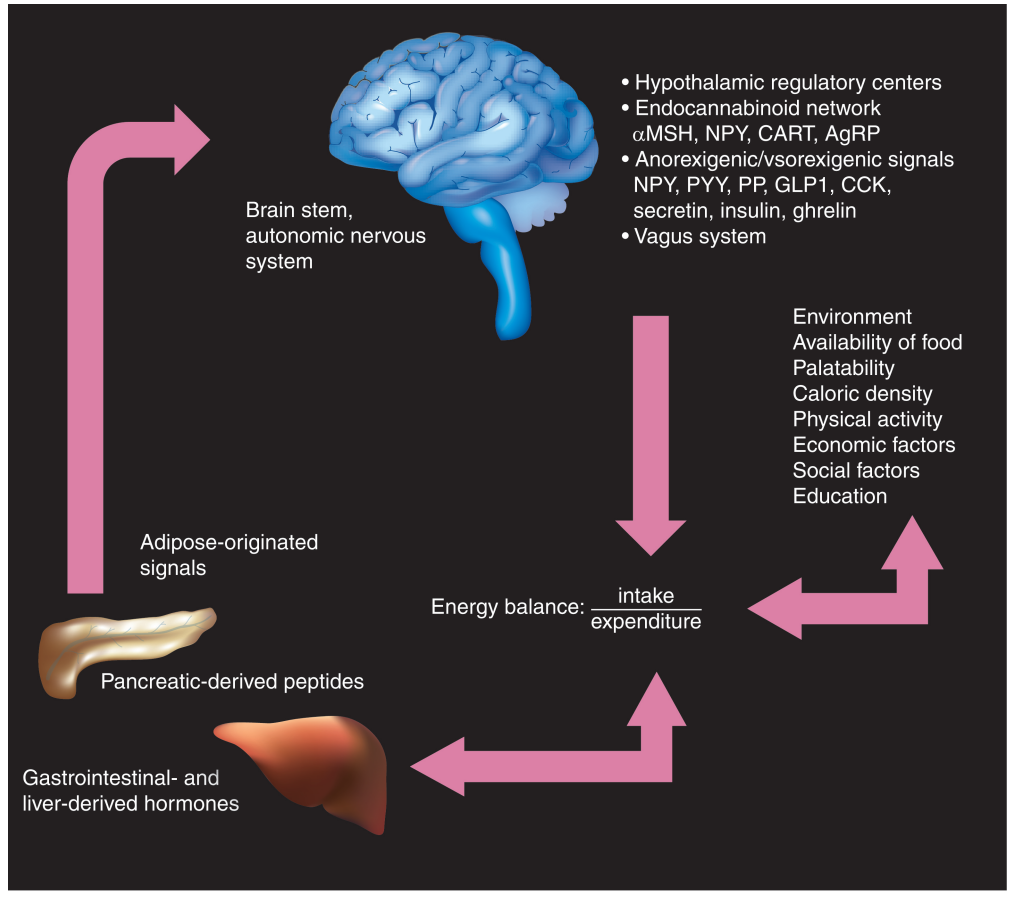
Gut hormones & their effect on weight

Current knowledge regarding the mechanisms implicated in the regulation of energy intake has led to the identification of numerous substances that affect weight. Several peptides produced and secreted in the gastrointestinal tract

Table 1. Overview of current medications used in the pharmacological management of obesity.

Agent	Efficacy (average weight loss) (kg)	Time studied (weeks)	Common side effects
Sibutramine	-4.45	52	Headache, dry mouth, insomnia, constipation, tachycardia, hypertension
Orlistat	-2.75	52	Diarrhea, flatulence, bloating, nausea and vomiting
Fluoxetine	Variable, could include weight gain	52	Anxiety, tremors, nausea, vomiting, insomnia, fatigue
Bupropion	-2.77	24–52	Dry mouth, diarrhea, constipation
Phentermine	-3.6	2–24	Tachycardia, hypertension, anxiety, insomnia, diarrhea, constipation
Sertraline	Variable	26	Nausea, headache, insomnia, dry mouth, diarrhea

Figure 2. Overview of the central and peripheral mechanisms that regulate appetite.



AgRP: Agouti-related protein; CCK: Cholecystokinine; GLP: Glucagon-like peptide; MSH: Melanocyte-stimulating hormone; NPY: Neuropeptide Y; PP: Pancreatic polypeptide; PYY: Peptide YY.

are currently known to influence appetite and food intake and can be used as therapeutic targets (**Figure 2**).

Ghrelin is a 28 amino-acid peptide with orexigenic properties, and has been demonstrated to be a short-term regulator of food intake in both experimental models and humans. The actions of ghrelin are mediated through interaction with specific G-protein-couple receptors. Acute administration of ghrelin (peripherally or in the CNS) increases caloric intake and weight in rodents [40], as well as in healthy humans when administered peripherally [41]. In the long term, ghrelin also appears to play a role, as it is significantly suppressed in obese individuals compared with lean subjects, normalizing after weight loss, either through diet and exercise, or bariatric surgery [42].

Glucagon-like peptide (GLP)-1, also produced in the gastrointestinal tract, is released after food intake, proportional to the amount of calories ingested, and stimulates glucose-stimulated insulin secretion, suppresses glucagon and slows gastric emptying. Similar effects appear to be elicited by oxyntomedullin, another naturally occurring peptide that currently gains importance as a potential therapeutic agent for the management of obesity [43]. GLP-1 acts like a satiety signal, and has both short- and long-term effects on energy balance. Intravenous GLP-1 induces postprandial satiety acutely in rodents [44]. Also, under experimental conditions, GLP-1 central infusion results in decreased food and caloric intake [45]. In humans, available studies indicate similar results with the use of peripherally administered GLP-1, in which the caloric intake is reduced by as much as 11.7%, in a dose-dependent manner [46]. Moreover, GLP-1 secretion appears to be reduced in human obesity, and is normalized after weight loss [47], while chronic GLP-1 therapy induces weight loss. GLP-1 analogs such as exenatide, as well as inhibitors of the enzyme responsible for its metabolism (dipeptydil peptidase IV; DPP-IV),

such as vildagliptin and sitagliptin, are currently being used for the management of DM2 and appear to have an acceptable effectiveness and safety profile [48]. While exenatide use results in moderate weight loss, DPP-IV inhibitors do not appear to affect weight, probably because they cause only mildly increased postprandial levels of GLP-1 [48].

Excitingly, there is evidence that GLP-1 is linked to increased β-cell mass in rodents, as well as reduced apoptosis and stimulation of differentiation of precursor cells into β-cells [49], which brings renewed hope for the treatment of DM2. However, the use of GLP-1 analogs as therapeutic agents is currently limited by the short life of the molecule, as well as the need for parenteral administration (subcutaneous in the case of exenatide) and high-dose-induced nausea and vomiting.

Cholecystokinine (CCK), derived mainly from the duodenum and jejunum, also increases postprandially and stimulates the secretion of pancreatic enzymes, increases intestinal motility and delays gastric emptying [50]. In early studies in rodents and humans, CCK decreases food intake [51]. These effects seem to be mediated through specific CCK G-protein-coupled receptors, which, upon inhibition, lead to increased caloric intake [52]. Interestingly, the short-lived modulatory action of CCK on appetite could interact with a long-lasting central leptin signal, which would result in a sustained effect on adipose tissue mass, and hence, on weight [53]. The use of CCK as a therapeutic agent for the treatment of obesity still awaits further studies that clarify the mechanisms involved in regulation of appetite and caloric intake.

Peptide YY (PYY), neuropeptide Y (NPY) and pancreatic polypeptide (PP) belong to the PP-fold peptide family, which share a similar tertiary structure. However, owing to specific structural characteristics, their biologic activities differ widely. PYY, derived mainly from the distal gastrointestinal tract, is found predominantly in an N-terminally-truncated form PYY (3–36), and, as opposed to PP, is able to cross the blood–brain barrier. The secretion of this hormone is increased after food intake and its peripheral administration results in decreased appetite in experimental models [54]. PYY actions also appear to be mediated through specific interactions with the G-protein-coupled receptors, whose activation also reduces food intake acutely [55]. After food intake, PYY levels rise, and plateau approximately 1–2 h later, the magnitude of increase is affected by the quantity of calories ingested, as well as the composition of the meal, being higher after fat ingestion relative to isocaloric intake of proteins or carbohydrates [56]. Interestingly, PYY levels increase before the meal reaches the distal parts of the gut that produce PYY, suggesting that the release of the peptide is mediated through neural reflexes, probably the vagus [56]. PYY appears to affect appetite via central actions and gut motility, leading to satiety [55]. Circulating levels of PYY are suppressed in patients with severe obesity, but they appear to be as sensitive as lean patients to the effect of peripherally administered PYY (3–36) [54], which suggests a potential therapeutic role for this peptide in the management of obesity.

Finally, PP is produced predominantly in the duodenal portion of the endocrine pancreas. PP is released in response to food intake and the amount secreted is proportional to the caloric intake. The secretion is typically lower during fasting state, and steadily increases during the different phases of digestion and subsequent meals, both in rodents and humans [57]. Studies in rodents have shown that overexpression of PP expression leads to reduced food intake and reduced body weight and delayed gastric emptying [58]. In humans, healthy subjects also display reduced food intake by approximately 22%, according to an experimental study by Batterham *et al.,* in which the effect was sustained for approximately 24 h after the intervention [57]. However, the relationship between PP and body weight in the long term is not always consistent and its role as a potential therapeutic agent for obesity still remains to be uncovered [59].

The emerging knowledge regarding the modulation of appetite, the participation of gut-derived hormones, their effects in the CNS and their interactions with signals originated in the adipose tissue will contribute to developing new strategies for the management of obesity.

The endocannabinoid system: an integrator of obesity & CMS?

Originating from early studies with *Cannabis Sativa*, main compound of the recreational drug marijuana, there has been an impressive progress in the knowledge about the endocannabinoid system in the pathophysiology of obesity and CMS during the last decades. This endogenous system is activated by stressful circumstances, such as pain and anxiety to induce sedation, but also stimulates appetite [60]. In addition, to

modulation of neuroprotection, nociception, motor activity regulation and memory processing [4,5], activation of this network appears to play an important role in the accumulation of visceral fat, development of obesity and the CMS [61].

Endocannabinoids derive from arachydonic acid, an essential FA belonging to Ω-6 family [62]. The most extensively studied cannabinoids are anandamide (arachydonoyl-ethanol-amide) and araquidonoil-glycerol [63]. These two molecules bind specific receptors located in areas of the hypothalamus functionally related to regulation of behavior.

Cannabinoids actions are mediated through specific receptors, cannabinoid receptor type 1 (CB1) and 2 (CB2) [64]. Both CB1 and CB2 are G-protein-coupled receptors [65], although the existence of other cannabinoids and/or ligands is possible. CB1 is highly expressed in hypothalamic areas of the brain related to regulation of behavior and appetite [66]. In addition, CB1 receptors are also found in peripheral tissues, including liver, muscle and adipose tissue, where they also participate in energy homeostasis [67]. CB1 receptors have also been identified in the pituitary [68], thyroid [69], adrenals and gonads [70]. In the gastrointestinal system, endogenous cannabinoids induce hunger sensation and, acting synergistically with hypothalamic signals, modulate food intake and adipogenesis [71].

Activation of cannabinoid receptors activates sterol regulatory element binding protein 1c (SRBP-1c) and associated enzymes, including acetyl CoA carboxylase (ACC-1) and FA synthase (FAS). Experimentally, CB1 agonists increase SRBP-1c mRNA, ACC-1 and FAS in liver tissue, leading to increased lipogenesis, fatty hepatic liver and hyperlipidemia. Moreover, cannabinoid stimulation leads to increased visceral fat, which is a characteristic of the CMS [72]. Cannabinoid stimulation in the hypothalamus induces hyperphagia, decreased basal metabolic rate and increased thermogenesis in experimental conditions [73]. These mentioned effects are abolished in animals treated with CB1 antagonists [74].

Therapeutic blockade of the endocannabinoid receptors

Studies have demonstrated hyperactivity of the endocannabinoid system in animals and obese humans. CB1 blockade chronically increases adiponectin levels, which in turn are associated with increased activity of AMPK, leading to reduced gluconeogenesis and increased FA oxidation, suggesting a beneficial effect on insulin sensitivity [75].

Rimonabant, originally designed in the 1990s for management of tachycardia in marijuana abusers, for antipsychotic therapy in schizophrenic patients and tobacco cessation, unexpectedly resulted in weight reduction sparking interest in these substances for the management of obesity.

From a clinical standpoint, the results obtained in clinical trials with Rimonabant are attractive [76–80]. The Rimonabant in Obesity (RIO) North America trial included 3040 obese/overweight patients with or without obesity-related comorbidities (except diabetes mellitus). RIO Europe, included 1507 obese/overweight patients in the same conditions. RIO lipids studied 1033 obese/overweight participants with dyslipidemia, excluding DM, and RIO diabetes included 1047 diabetic overweight and/or obese patients. Collectively, the results of these studies demonstrate a significant reduction in weight (~5–10%) and WC, increased HDL levels, reduced triglycerides, systolic blood pressure total cholesterol, and a reduction in the proportion of atherogenic small and dense LDL, without affecting LDL cholesterol.

Importantly, fasting glycemia and response to insulin also improved and adiponectin levels were 50% higher than values predicted by weight reduction alone. CRP, a marker of inflammation and predictor of CVD risk, was decreased and the number of patients who, on admission, had features consistent with CMS was also decreased at the end of the trials (**Table 1**) [76–80]. The most frequent adverse reactions related to CB1 blockers in these studies were nausea, vomiting, anxiety and depression.

CB1 blockers emerge currently as an attractive option in the management of cardiometabolic risk factors. Treatment produced in the aforementioned trials resulted in a significant improvement of lipid profile, glucose homeostasis and insulin resistance markers, which was independent from the weight loss effect. Instead, these beneficial effects appear to be mediated via increase in adiponectin [78]. Concern regarding the endocannabinoid network derives from the observation that marijuana abuse has been related to increased appetite, as well as increased blood pressure, high triglycerides and low HDL. A recent study by Redondi *et al.* studied 1365 patients with history of marijuana use, included in the Coronary Artery Risk Development in Young Adults (CARDIA) study [81]. Multivariate analysis showed that the use of marijuana was not significantly associated with CVD risk factors (systolic blood pressure and triglycerides).

Marijuana use, however, was associated with high caloric diet, tobacco abuse and other recreational substance abuse, which could have an effect on long-term CVD risk profile.

Currently, the CB1 antagonist rimonabant is marketed in Europe and some countries in Latin America; however, its use has not been approved by the US FDA. Further research in this exciting area is warranted and newer medications, more specific and with the ability to modulate appetite without affecting other systems and functions, such as mood, will result in a potent therapeutic alternative in the future. Indeed, some of the beneficial effects of the CB1 blockade demonstrated in the RIO studies exceed what could be expected with weight loss alone, and are related to modulation of adiponectin. Additional studies specifically directed at Hispanic populations, in which adiponectin biologic behavior varies, will clarify the role of the endocannabinoid network in the pathogenesis and management of the CMS in these heterogeneous populations.

Expert commentary & future perspective

Obesity, the epidemic of the new millennium, is rapidly increasing worldwide and is largely driving the dramatic increase of the clustering of CVD risk factors that define the CMS. However, the biologic behavior of obesity and CMS appears to vary in different populations. Hispanic populations appear to be at particularly increased risk for CMS and poor long-term outcomes in terms of morbidity and mortality, a phenomenon that appears to be largely related to higher rates of poverty and unfavorable environment. In addition, new knowledge regarding the mechanisms of adipogenesis and energy homeostasis suggests specific pathophysiologic differences between Hispanic and other populations, such as biology of adiponectin and other adipokines.

However, the widespread but frequently overlooked variability of the Hispanic or Latino population makes it particularly challenging to clarify the real epidemiological, clinical and pathophysiological characteristics of obesity, DM2 and CMS in these populations. As a result, specific studies evaluating the role of currently available and emerging therapeutic strategies in Hispanics are also lacking. New studies evaluating all these aspects of obesity in Hispanics are certainly needed and when added to improved social, economical and healthcare conditions, will undoubtedly contribute to at least partially reduce the main burden of the CMS: morbidity and mortality from CVD.

Financial disclosure

The authors have no relevant financial interests, including employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties related to this manuscript.

Executive summary

- Obesity and the cardiometabolic syndrome are a fast-growing pandemic in the modern world.
- There is an extreme diversity in the Hispanic population.
- Some pathophysiologic elements of obesity and the cardiometabolic syndrome behave differently in Hispanics compared with non-Hispanic populations.
- Treament of obesity does not differ in Hispanics compared with non-Hispanics, owing to lack of studies targeted specifically to Hispanic populations.
- More data are required regarding the epidemiology, pathogenesis and management of obesity and cardiometabolic syndrome in Hispanics.

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