Cardiovascular Risk and the Endocannabinoid System

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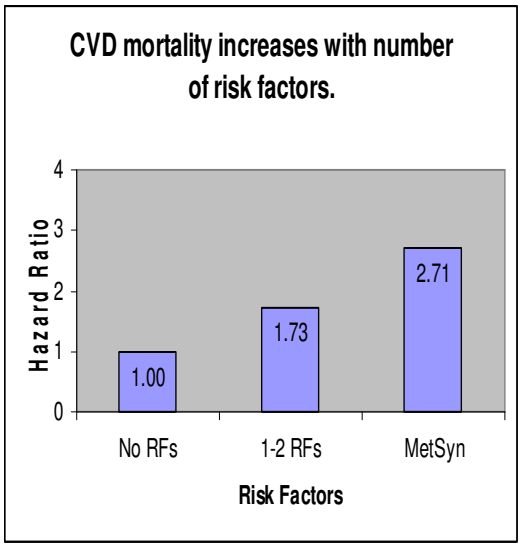
A number of studies and analyses have illustrated the increased rate of cardiovascular disease conferred by multiple risk factors.[1,2] Up to now, however, the primary focus for addressing cardiovascular risk has been the treatment of each risk factor separately (e.g., LDL cholesterol, hypertension, and diabetes). Major gaps in our overall understanding of the ways in which these individual risk factors act together in creating an increased cardiovascular risk exist. Still, an emerging focus on the additive nature of multiple risks has led to an effort to reduce the overall number of risk factors and evaluate the relative strength of the effect of each on the others. The development of the metabolic syndrome (defined as the presence of three or more of five individual risk factors including elevated triglycerides, low levels of HDL-C, elevated blood pressure, expanded waist circumference, and borderline elevated glucose or diabetes) represents a notable example of a more global risk factor assessment (Figure 1).[3]

The Role of Visceral Adiposity

In searching for a place to start, obesity, perhaps more than any other single risk, plays the central role in overall cardiometabolic risk. In fact, obesity appears to be a major driver of insulin resistance, which in turn, can result in dyslipidemia, hypertension, inflammation, and even glucose intolerance and diabetes.[4] A case can be made that obesity is the risk factor that drives the entire metabolic syndrome.

Figure 1. Cardiovascular mortality increases with number of risk factors.

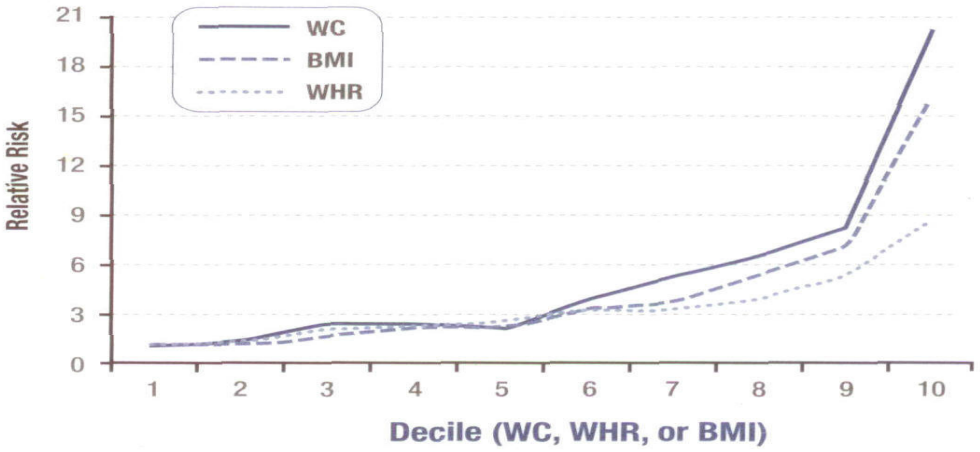


It is important to recognize that not all fat is created equal. The International Diabetes Foundation (IDF) identified *visceral* obesity as the most critical cardiovascular risk.[5] Abdominal obesity appears to be a greater predictor of non-insulin-dependent diabetes mellitus (NIDDM) than overall obesity (Figure 2).[6] Indeed, visceral adiposity (not overall obesity) appears to be the primary predictor of both NIDDM and the metabolic syndrome in general.[7-9]

The Endocannabinoid System

In the midst of research on cardiovascular risks and visceral adiposity, a previously little known physiologic system has been identified that appears to play a major role in the co-regulation of interactions between fat and other physiologic systems. First suggested during the recognition of the

Figure 2. Age-adjusted relative risk of Type 2 diabetes by baseline waist circumference (WC), waist-to-hip ratio (WHR), and BMI deciles.



appetite-inducing properties of the cannabinoid, Cannabis Sativa,[10] the endocannabinoid system (ECS) was not well understood until the discovery of endogenous cannabinoids (ECs) and their receptors. Despite this late start, the last twenty years has seen a remarkable increase in researchers' understanding of the structure and vital function of the ECS.

The initial discovery of where cannabinoids bind to sites in the brain of rats was followed by the discovery of two endogenously-produced cannabinoids, anandamide and 2-arachinodonyl glycerol. The binding sites for these cannabinoids include the CB1 receptor, which is involved in the regulation of energy homeostasis, and the CB2 receptor, which is found primarily in the immune system and is not thought to play a significant role in feeding or energy balancing.[11]

Once these basic elements of the ECS were described, research turned to how the system functions. The CB1 receptors are activated by endocannabinoids, which are arachidonic-acid derivatives that are synthesized as needed, then bind to the CB1 receptors. Upon binding, they activate the system, then rapidly degrade. Endocannabinoid production and binding with CB1 receptors modulates energy balance and metabolism in the brain and also is active in adipose tissue, the liver, skeletal muscle, and the gut.[12]

Centrally, CB1 activation stimulates food intake directly by increasing the motivation to eat and the sensory appeal of food.[13] In addition, CB1 receptors in the hypothalamus appear to participate in hunger and satiety signaling.[13] The direct evidence of this central activation of the system came with the injection of the endocannabinoid anandamide directly into the brain of pre-fed and satiated rats. When the ventromedial hypothalamus was stimulated in this fashion, the rats significantly overate.[14] Having demonstrated that central nervous system (CNS) stimulation can bolster food intake, genetically engineered CB1 receptor-deficient mice were underfed, and unlike their normal wild-type littermates, the receptor-deficient mice ate far less when exposed to food.[15] When rimonabant, a CB1 antagonist, was added to the daily regimen of obese, overfed mice, body

weight was reduced. This confirmed that the endocannabinoid system, when stimulated, plays a critical role in the development of obesity.[15]

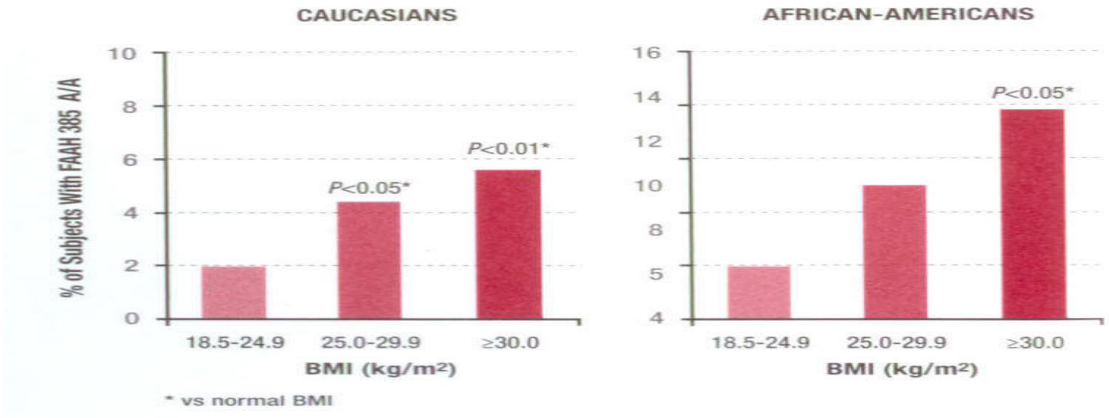
In addition to the effects on the CNS, the actions of the endocannabinoid system have been found in peripheral tissues, where ECS stimulation is believed to modulate a number of other mechanisms. In the liver, CB1 stimulation appears to facilitate the formation and storage of triglycerides and to promote lipogenesis and the formation of fatty liver.[16] In the GI tract, cannabinoid and ghrelin levels increase together in response to fasting. When the endocannabinoid antagonist rimonabant is intraperitoneally injected, it has the effect of decreasing endocannabinoid and ghrelin levels, thereby reducing hunger signals.[16] In addition to these effects, blockade of CB1 receptors appears to upregulate the critically important plasma protein adiponectin positively, which in turn decreases hyperinsulinemia and weight.[17]

ECS in Humans

Not surprisingly, considering these animal studies, human data indicate that higher levels of endocannabinoids are found in obese humans when compared to their lean counterparts. In fact, compared to lean subjects, both anandamide and 2-AG have been found in significantly higher quantities in obese women.[18] Further studies need to be conducted to ensure these findings apply to men. It is interesting, and perhaps not unexpected given the difficulty of maintaining weight loss, that endocannabinoid levels have not been found to decrease during weight loss.

Further evidence of the action of the ECS in promoting human obesity comes from the discovery of a genetic deficiency caused by a missense mutation in fatty acid amide hydrolase (FAAH; an enzyme that helps degrade endocannabinoids). With a deficiency in FAAH, higher circulating levels of the endocannabinoids and a significant increase in the likelihood of obesity are noted (Figure 3).[19] In addition, a study comparing levels of endocannabinoids in human subcutaneous and visceral fatty tissues revealed the presence of higher levels of endocannabinoids in visceral fatty tissue, reinforcing the importance of the ECS in preferentially modulating the most important human depot of fatty tissue: visceral fat.[20]

Figure 3. Percentage of subjects with increasing percentage presence of FAAH missense by Body Mass Index.



The ECS in the Development of Cardiometabolic Risk

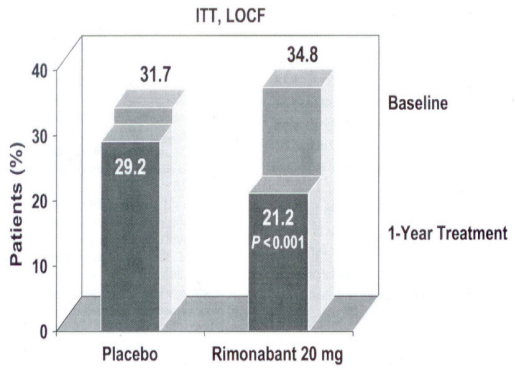
Emerging evidence suggests that stimulation of the ECS centrally and peripherally leads to increased food intake, increased waist circumference (indicative of increased visceral adiposity), elevated triglycerides, decreased HDL-cholesterol, and insulin resistance. Recent phase 3 trials on the ECS antagonist rimonabant have demonstrated its ability to block the central and peripheral effects of the ECS. In four phase 3 clinical trials, rimonabant was not only associated with significant weight loss, but also with a decreased waist circumference and improved glucose tolerance.[21-24] Interestingly, the improvement in HbA_{1c} in the Rimonabant-in-Obesity (RIO) Diabetes trial was much greater than would have been predicted by the degree of weight loss achieved.[21]

With additional benefits noted in triglyceride levels, HDL-C and blood pressure[21-24], rimonabant achieved a significant decline in a number of individual risk factors and in the prevalence of the overall metabolic syndrome (Figure 4).[23] However, a major obstacle to approval of rimbonant in the United States is the Food and Drug Administration Advisory Committee's recommendation that approval be delayed, pending resolution of safety issues concerning increased levels of depression and suicide ideation.[25]

Summary

In the search for better ways to prevent and treat cardiovascular disease, notation of multiple risk factors and the central role that visceral adiposity plays in modulating overall risk are important. The challenge of reducing this risk has led to a search for ways to reduce adiposity consistently and efficiently while positively impacting other classic cardiovascular risks. The discovery of the ECS and the ability to block the effects of its over-stimulation gives a new approach to reduce multiple cardiometabolic risk factors significantly. With continued efforts to improve the lifestyles of our patients, combined with exciting new pathways for pharmacologic intervention, we can achieve the reduction in cardiovascular risks needed to tame the epidemic of obesity-mediated cardiovascular disease.

Figure 4. Change from baseline in metabolic syndrome status at one year.



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