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Chapter

Sex Differences in Obesity-Induced Inflammation

Sari Terrazas, Lauren Brashear, Anna-Katherine Escoto, Shannon Lynch, Dylan Slaughter, Neena Xavier, Norman Robert Estes II and Samantha Giordano-Mooga

Abstract

Obesity is defined as a BMI greater than 25 kg/m^2. Once thought to simply be a nutritional disorder, obesity has become a major health concern characterized by a state of constant low-grade inflammation caused by chronic adiposity. This state of inflammation is characterized by circulating inflammatory mediators, such as IL-6, leptin, and TNF-α, as well as varying levels of glucose-regulating hormones produced by obese adipose tissue. When left untreated, obesity can lead to a number of diseases including, but not limited to, cardiovascular disease, metabolic syndrome, neurodegeneration, type II diabetes mellitus, chronic kidney disease, and infertility. The distribution of adiposity differs in men and women, and these differences, along with the differences in sex hormones and sex hormone levels, can exacerbate or attenuate the course of disease pathology. Obesity can also be exacerbated by stress, which can worsen disease pathogenesis. In this review, we will explore how obesity affects inflammation and disease and how sex can affect the course of these diseases.

Keywords: obesity, inflammation, sex differences, estrogen, testosterone

1. Introduction

Approximately 70% of the US adult population is considered overweight or obese [1]. Obesity has been associated with an elevated risk of type II diabetes, cancer, neurodegeneration, infertility and stress hypertension, and cardiovascular disease (CVD) [2, 3]. The increased risk for various health risks is due in part to the inflammatory adipokines produced by the adipose tissue itself. Clinically, body mass index (BMI) is the most widely used tool to measure adiposity. However, BMI measures total mass, including both fat and fat-free (lean) mass, so it is a poor indicator of adiposity [2]. Further, the different compartments of fat and different types of adipose tissue within these compartments play a major role in the overall increased health risks associated with increases in adiposity [4]. Lastly, the body composition differs between men and women; men have more lean mass than women, whereas women have more fat mass. In this book chapter, we help to unravel the differences in adipose-induced inflammation in men and women and how these differences may contribute to various pathophysiologies.

2. Adipose tissue

Adipose tissue is composed of a variety of cells, including adipocytes, macrophages, leukocytes, endothelial cells, and fibroblasts. This metabolic tissue and the subsets of cells found within this tissue play a role in both the inflammatory and hormonal pathways. This has led many to believe that adipose tissue is a novel endocrine organ [5].

Classically adipocytes were believed to be either white or brown adipocytes. The white adipose tissue (WAT) is the adipose tissue which is often focused on in obesity research. The WAT is less metabolically active, is composed primarily of stored triglycerides, and produces adipokines which regulate hunger, satiation via leptin, breakdown of triglycerides via adiponectin, and insulin sensitivity via IL-1 and IL-6 [5]. WAT has also been associated with inflammatory adipokine production, including TNF-alpha, MCP-1, resistin, and IL-6 [5]. Interestingly, these adipokines become dysregulated in obese states which can further exacerbate cellular and systemic dysfunctions [6]. The increase in inflammatory cytokines is a contributing factor to the various pathophysiologies discussed within this chapter.

Brown adipose tissue (BAT) is colored brown due to the high mitochondrial content. This highly metabolically active tissue also plays a role in thermogenesis, classically in neonates, and in lipid breakdown [7]. Key features of BAT include the high levels of mitochondria and the presence of uncoupling protein 1 (UCP-1), which both play a role in the "extraction" of nutrients from free fatty acids and triglycerides [8, 9]. Recent studies have shown that BAT is not only found in neonates but can also be found in adults. A study conducted in males and females using PET-CT scans detected BAT tissue in the fascial plane in the ventral trunk and superficial and lateral sternocleidomastoid muscles [10]. Further, this study showed that there were differences in BAT mass in males and females, with females having more BAT than males. There was also an inverse correlation in BAT detection with age and BMI in older patients [10]. The data of this study suggest that shifting WAT to BAT also known as "beiging WAT" or increasing BAT production may be an effective treatment against obesity [11].

3. Sex differences in hormones and adipose tissue

The sex hormones, most notably testosterone (androgen) in males and estrogen and progesterone in females, play a role in fat deposition, metabolism, and energy balance within their respective sex. We will briefly discuss the specific roles of the sex hormones as they relate to adipose tissue. Estrogen has been shown to have both anti-inflammatory and antioxidant properties and can regulate metabolism [12]. Much of the data supporting estrogen as a protective factor comes from differences observed between pre- and postmenopausal women, where women in the premenopausal phase are protected against many cardiometabolic diseases, until they reach the menopausal period, where there is an increase in CVDs, inflammation, and weight gain [13]. Low testosterone levels in men have also been associated as a risk factor for pathophysiologies, including sexual dysfunction, CVD, insulin sensitivity, and type II diabetes [14].

Conversely, high levels of estrogen in men and high levels of testosterone in women have been shown to have negative effects on weight gain [15]. High levels of testosterone, seen in women with polycystic ovarian syndrome (PCOS), or low levels of estrogen seen in postmenopausal women have been linked to increased weight gain, specifically in the intra-abdominal fat [16]. Further, in men, testosterone

replacement, when there are low levels of testosterone, has been shown to increase lean body mass and improve lipid and cholesterol levels [17, 18].

More recent studies have shown that while both estrogen and androgens are important for many physiological processes, the estrogen to androgen ratio is important in regulating adipose tissue deposition. Interestingly in a study looking at the effects of testosterone replacement therapy, men with the lowest levels of estrogen (<10 pg./mL) had the largest decrease in body fat reduction after 6 months of testosterone therapy [19]. An important step in the production of estrogen is the enzyme aromatase, which converts testosterone to estrogen. Both male and female aromatase null mice exhibited increased weight gain and obesity-related metabolic complications [20]. Together, these data suggest that both estrogen and testosterone play an important role in regulating obesity and adiposity.

As stated previously, the body composition differs between men and women. Men are more likely to accumulate adipose tissue around the trunk and abdomen, whereas women usually accumulate adipose tissue around the hips and thighs [21, 22]. Women have a higher percentage of body fat than lean fat when compared to men who have the same BMI. Therefore, the health consequences are different for each gender at the same BMI [21]. In addition, a higher portion of that fat is in the femoral-gluteal region as compared to the abdominal region for men [22]. Studies have shown that the relative distribution of fat has a greater impact on CVD risks than total excess body fat. The female pattern of fat distribution, around the femoral-gluteal area, is relatively protective, compared to the male pattern of abdominal fat accumulation [23–25].

Within the abdomen, fat can accumulate in the subcutaneous area, subcutaneous adipose tissue (SAT), or, in the deep abdomen, visceral adipose tissue (VAT). Both VAT and SAT, in the obese state, produce increased inflammatory cytokines, including TNF-α and IL-6, which produce increased levels of leptin and decreased levels of adiponectin [26, 27]. These changes can cause further inflammatory cascades, including inducing proinflammatory macrophages into the adipose tissue (**Figure 1**).

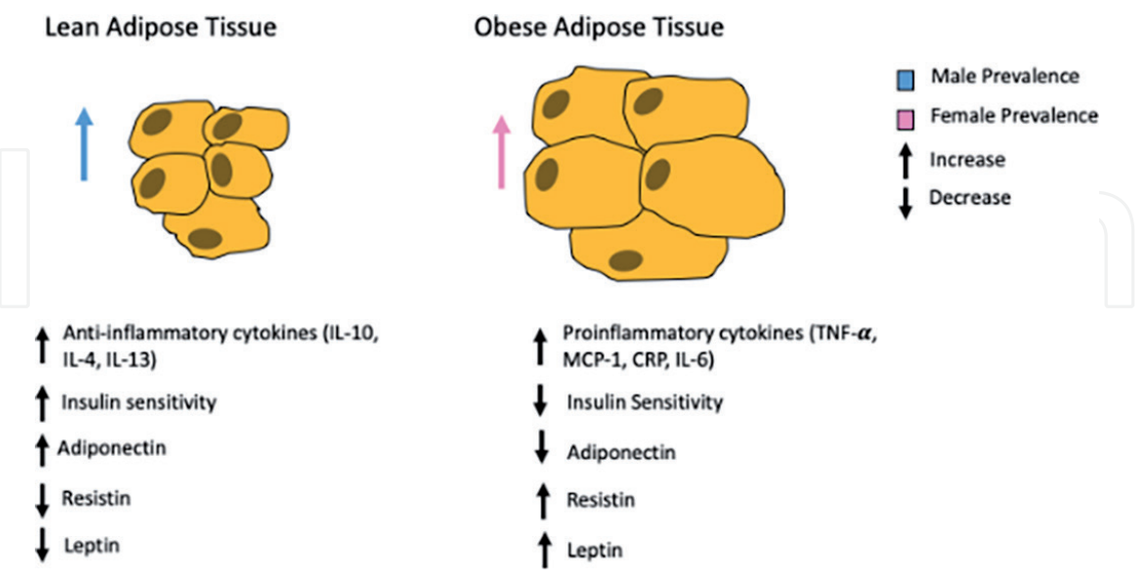

Figure 1.
The effects of lean vs. obese adipose tissue. A healthy diet and exercise are characterized by lean adipose tissue. Lean adipose tissue aids in regulating inflammation by secreting anti-inflammatory cytokines as well as secreting high levels of adiponectin which aids in insulin sensitivity [27]. Leaner adipose tissue also secretes low levels of leptin and resistin. Conversely, obese adipose tissue release high levels of resistin and leptin which promote insulin insensitivity. Obese adipose tissue also exhibits a proinflammatory cytokine profile which can lead to diseases such as diabetes and neurodegeneration. Men tend to have a greater ratio of lean to obese adipose tissue since they have greater muscle mass compared to women who have more obese adipose tissue [28].

These inflammatory cells exacerbate adipose tissue cytokine production or increase disease risks, which can further feed into this cycle.

Multiple studies have also shown that VAT is associated with a higher cardiovascular risk [24, 25]. Since the VAT has primarily been associated with the abdominal region, the VAT has historically played a more pathogenic role in male pathology. Because of the high rate of obesity in the United States, and the increased VAT deposition seen in both men and women, we understand that VAT deposition also increases risks in females. Therefore, more therapeutic interventions are needed to inhibit VAT deposition in both men and women.

4. Gender-specific differences in aging due to inflammation

Considerable amounts of data indicate that sex-specific differences in both acute and chronic inflammatory responses exist between males and females across multiple species and that these differences are altered with advancing age. Various studies suggest that these sex-specific variances include differences in multiple inflammatory biomarkers, including TNF-alpha, IL-6, IL-10, and C-reactive protein (CRP) [29]. While it appears clear that variations between the sexes do exist and these variations change with aging, the exact fluctuations in inflammatory biomarkers, both between sexes and with aging, are not fully elucidated.

Complicating matters is the established role of adipose tissue as a source of both pro- and anti-inflammatory cytokines. Leptin, adiponectin, and other cytokines synthesized and secreted by adipose tissue have been shown to play a profound role in modulating both systemic and localized inflammatory reactions. Adipose tissue likely plays a role as a source of pro- and anti-inflammatory cytokines and since, as previously described, males and females accumulate adipose tissue in different/store body fat in different locations, the adipose tissue plays an important role in the sex-specific differences in inflammatory responses, especially with aging.

Another complicating factor regarding inflammatory responses between males and females is the potential role of steroid hormones in various sex-specific physiological responses, including accumulation and storage of adipose tissue, and inflammation. Estrogen has been shown to have potent anti-inflammatory activity and cardioprotective effects in females, and as estrogen levels decline with age after the onset of menopause, these protective effects of estrogen are minimized [12, 30]. While much has been determined, further study into the sex-specific differences between males and females, how these levels change over time with aging in a sex-specific manner, and the role that these levels and their changes play in both acute and chronic diseases are warranted.

Many biomarkers of inflammation have been investigated regarding adiposity, age, sex, and ethnic variations. The most studied biomarkers include C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-alpha). Data from a meta-analysis investigating potential relationships between the adipose tissue-derived cytokines leptin and adiponectin and inflammatory biomarkers including CRP, IL-6, and TNF-alpha suggested a positive correlation between leptin and all three inflammatory biomarkers, whereas there was a negative correlation with respect to adiponectin and the biomarkers [31]. When adjusted for age, Grassman et al. observed that correlations weakened as the age of the participants increased. In contrast to other studies, the authors found no significant differences when looking at sex and inflammatory markers in relation to adipose tissue. In another study aimed at elucidating mechanisms responsible for differences in inflammatory responses across sexes, Wegner et al. found that proinflammatory responses to endotoxin in women were greater compared to

men, with significantly higher increases in plasma TNF-alpha and IL-6 [32]. Interestingly, increases in circulating plasma cortisol levels were also found to be significantly elevated in women as compared to men, which could play a role in the heightened response.

In contrast Kuo et al. used endotoxin exposure in young (5–6 weeks) versus adult (9–10 weeks) male and female mice to investigate relationships in the inflammatory responses in these groups [33]. Older male mice showed significantly higher levels of pro-inflammatory markers IL-6, IL-10, and TNF-alpha than age-matched female mice upon stimulation with endotoxin. In younger mice, however, they did not find a gender-specific difference in these same biomarkers. An investigation of factors associated with biomarkers of systemic inflammation using age-, sex-, and body mass index (BMI)-adjusted linear regression found an age-related effect on the markers. They examined multiple factors in relation to inflammatory biomarkers including CRP, IL1β, IL6, IL8, and TNFα in adults between the ages of 50 and 76 years. The results of this study indicated that age influenced circulating concentrations of all biomarkers except IL1β, with increasing age being associated with higher concentrations of all other biomarkers tested [34]. When they looked at sex-specific differences, the results were varied, with CRP and IL-6 levels being lower among men.

In looking at sex-specific differences of oxidative stress and inflammation with regard to cardiovascular risk factors in Arab populations, Khadir et al. found that females had higher levels of reactive oxygen species (ROS) and CRP after adjustment for body mass index (BMI) and waist circumference [35]. Conversely, males had increased levels of IL-6, IL-8, and TNF-alpha. In order to look at the relative impact of central obesity versus general obesity, the authors adjusted for age, BMI, and gender and noted that the levels of IL-6, TNF-alpha, and ROS were associated with central obesity but not general obesity, further suggesting that sex-specific patterns of adipose distribution can potentially account for some of the observed sex-specific differences in males versus females. The authors concluded that the relative contribution of inflammation and oxidative stress to CVD in Arab populations was linked, at least in part, to gender-specific distributions of body fat [35].

5. Sex differences in obesity-induced inflammation in pathology

While it is well known that obesity is a risk factor for many diseases, it is important to understand that the chronic state of inflammation associated with obesity further exacerbates obesity itself. Therefore, in many cases, obesity and inflammation increase pathophysiology, and these pathophysiologies further exacerbate the inflammation and obesity in a continuous vicious cycle. It is important to understand the role of sex and the sex hormones in this vicious cycle in order for better/more effective treatments and treatment plans for obese patients with various pathophysiologies. Below we describe the role of the sex hormones on obesity-induced inflammation in metabolic syndrome, CVD, type II diabetes, chronic kidney disease (CKD), neurodegeneration, cancer, infertility, and stress.

5.1 Metabolic syndrome

Metabolic syndrome (MetS), also known as syndrome x, is a health condition characterized by insulin resistance, glucose intolerance, hypertension, high triglycerides, low HDL cholesterol, abdominal obesity, dyslipidemia, and inflammation [36]. The increased incidence of MetS has been linked to obesity and a lack of

physical activity [37]. According to the Centers for Disease Control (CDC), a review of the NHANES data shows that as of 2012 more than one-third of US adults were considered to have MetS [38]. MetS affects over 30% of people by the time they reach age 65, and these statistics are expected to rise in the upcoming years [26]. By simply losing 5–10% of body weight, risk of developing metabolic syndrome, CVD, and type 2 diabetes is reduced significantly [26]. This emphasizes that prevention, rather than treatment, is the key to reducing the prevalence of metabolic syndrome in those at risk and those who are pre-symptomatic.

Diagnostic criteria for metabolic syndrome vary among organizations but typically include blood pressure, a large waist circumference, and the following: high levels of triglycerides and blood glucose and low levels of high-density lipoprotein cholesterol [26, 37, 39]. Previous diagnoses relied on body mass index; however, this has recently shifted to favor waist circumference because of its role in identifying central/abdominal obesity [36]. As previously described in this chapter, abdominal/central obesity, with increased VAT, has been associated with increased risks for disease and inflammation.

Interestingly, there is no difference in prevalence of MetS between men and women, but there are differences in symptoms among men and women; women are more likely to have abdominal obesity, whereas men have more varied symptoms [36]. As previously described, intra-abdominal obesity is not classically associated with women and, therefore, may play a more pronounced role in this gender. Further, it has been shown that women throughout their lives have consistently higher levels of adiponectin which increases insulin sensitivity and leptin, which signals fullness to the brain than males. This implies that the adipose tissue in women produces adipokines which play a role in female adipose deposition and regulation [40–43].

It is well known that brown adipose tissue (BAT) is characterized by the expression of UCP-1 which causes an increase in mitochondrial function and metabolism [44, 45]. UCP-1 has been linked to the "beiging of WAT" and a more metabolically active tissue. Further, in oxidative phosphorylation, genes, responsible for assisting in transcriptional activation in the mitochondria, have increased levels of expression in women [41]. The upregulation of this UCP-1 and increases in oxidative phosphorylation genes indicate that women express more metabolically active fat mass in comparison to men. Understanding that women have more metabolically active fat may help to explain the differing symptoms seen in MetS between men and women.

MetS and obesity can induce changes in gene expression. PPAR γ is one of the hormone receptors responsible for regulating adipocyte differentiation and lipolysis. Genetic SNP predispositions within this receptor, which are found in women, have been linked to increased susceptibility for obesity and insulin resistance [46] Estrogen can also activate a variety of metabolism genes, which play a role in the increased fat metabolism in humans and rodents [44, 47]. Women in the postmenopausal period, when estrogen levels have decreased, have a higher incidence in central adiposity and a higher risk for developing MetS [48]. Contrastingly, throughout life men have larger muscle mass and less free fat in organs that are highly metabolically active like the kidneys, liver, and brain. Males are more likely than women to experience an increase in incidence of diabetes due to decreases in insulin sensitivity [46]. Men also have lower expression of oxidative phosphorylation genes and brown adipose tissue, as indicated by UCP1, compared to women [49]. Taken together, these data support the idea that men and women present with different symptoms of metabolic syndrome and, therefore, may need different treatments for MetS consistent with these symptoms.

5.2 Cardiovascular disease

According to the American Heart Association, CVD is a term that encompasses many conditions including heart disease, heart valve issues, heart failure, and stroke. CVD is the leading cause of death for a variety of US ethnic populations [50]. Risk factors include metabolic syndrome, high blood lipid and glucose levels, high blood pressure, central/abdominal adiposity, low HDL, and high LDL cholesterol [46]. Further, there are differences in the prevalence of CVD among race, sex, and hormone levels [50]. Classically, men have higher levels of CVD than women, until women reach the postmenopausal period, the sixth decade of life, where women have similar or higher incidence of CVD than males of the same age [50].

Obesity, specifically abdominal adiposity, is a main risk factor for CVD. The Framingham Heart Study, a long-term observational study, determined that obesity increases cardiovascular disorders by 64% for women and 46% for men [51]. Further, Garcia et al. have shown that obesity more greatly impacts women's risk and incidence of CVD than men [52]. Therefore, reducing and preventing obesity could be a critical method for mitigating cardiovascular-related disorders in both men and women.

Fat accumulation of the neck has been found to be a strong predictor of CVD [53]. Fat accumulation is usually estimated via the measuring the neck circumference. In contrast to the well-defined and studied compartments and sex differences in accumulation with the abdominal fat deposition, less is known about these factors in the neck. In one retrospective study, overweight and obese women have more subcutaneous neck fat compared to men even after age and BMI matching. In the same study, subcutaneous neck fat was associated with higher incidence of metabolic risk than intermuscular fat deposits in both sexes [54]. This suggests that similar to abdominal fat, women have more subcutaneous fat and men more intermuscular fat in the neck.

Obesity creates an inflammatory state of the body that affects heart health. However, the overall effects may differ among the sexes based on sex hormone activity. Men have a higher overall incidence of death due to CVD [50]. The X chromosome in men upregulates the expression of genes responsible for functions of cell death mechanisms and cellular trafficking/migration, while the Y chromosome is responsible for genes involved in innate immunity activation. Activating the innate immune system, specifically the immune cell, the macrophages, induces inflammation and increases the risk for developing atherosclerosis [46]. Therefore, by inheriting a Y chromosome, men increase their genetic risk for developing CVD. Data suggests that testosterone does not confer any protection against obesity, inflammation, and CVD [46].

Levels of the sex hormone estrogen do not appear to affect men as severely as women [46]. It is hypothesized that the gender difference of varying estrogen levels only becomes evident in postmenopausal women who have lower levels of this sex hormone. Treatment and prevention methods using statins for CVD have been targeted more at men than women, as deemed appropriate by the American Heart Association. However, guidelines have recently been tailored to be more gender-inclusive based on cardiovascular risk factor assessments [52]. Sex differences attributed to genetic factors and lifestyle habits lead women to be more susceptible to CVD with elevated risk if preventative methods are not taken. Sex differences in CVD arise as the result of a combination of effects from various genetic and environmental factors.

Another important sex difference in CVD is the effect of the sex hormone estrogen. Circulating levels of estrogen fluctuate during a woman's life span and can regulate inflammation. Inflammation increases cardiovascular risk, as indicated

by increased levels of C-reactive protein [52]. CRP is both an inflammatory protein and an important biomarker of cardiovascular damage. It is hypothesized that the higher levels of systemic estrogen, associated with pre-menopausal women, have been shown to have a cardioprotective effect and reduce inflammation. The Women's Health Initiative designed a study to determine the possible use of hormone therapy as a preventative measure against CVD in postmenopausal women. The initial trials were ended early due by the Data Safety Monitoring Board (DSMB) due to the increased incidence of stroke and breast cancer in the estrogen + progesterone arm of the trial [55]. Further analysis of this randomized control study ultimately provided evidence for a concept known as the "timing hypothesis." This hypothesis states that hormone replacement therapy near the onset of menopause, within 5 years, may lower the risk for CVD, while MHT treatment in women greater than 5 years from menopause is harmful [56]. The timing hypothesis has had an important impact in clinical settings [30].

Traditional CVD risk factors that are increased for women include lack of physical activity, smoking, diabetes, obesity, dyslipidemia, and hypertension. Many of these risk factors are highly prevalent in the United States, meaning comorbidities are associated with CVD. For example, every two in three adults are overweight or obese, highly increasing their risk to develop CVD as well as other conditions [52]. These risk factors are preventable and reducible by means of lifestyle changes such as eating a healthy diet and maintaining exercise. Some nontraditional risk factors for women CVD include the following: depression, autoimmune diseases, treatment for breast cancer, hypertensive pregnancy disorders, gestational diabetes, delivering a preterm child, and ischemic heart disease [52]. It is hypothesized that women with ischemic heart disease have higher mortality rates and worse CVD outcomes than men due to insufficient detection and treatment options.

One method to improve adipose deposition detection is through imaging, as advancements in technology have allowed for detailed assessment of subcutaneous and visceral fat compartments. Computed topography (CT) and magnetic resonance imaging (MRI) are considered the gold standard for detailed assessment of body composition. However, these tests are expensive, not readily available, and, in the case of CT, associated with a significant dose of radiation. Dual-energy X-ray absorptiometry (DXA) is a technique used for osteoporosis screening and more readily available and less expensive and has relatively minimal radiation exposure. Therefore, it is more often used as it is able to assess body composition, such as fat and lean mass, and can quantify VAT and SAT accurately in obese patients [57, 58]. Fox et al. examined over 3000 subjects from the Framingham Heart Cohort who underwent CT of the abdomen [59]. They demonstrated a significant association between abdominal SAT and VAT in men and women and increased risk of hypertension, diabetes mellitus type 2, and metabolic syndrome. There was a stronger correlation with VAT and most of the cardiovascular risk factors. Interestingly, there were significant sex interactions with increasing volumes of SAT and VAT. Increasing volumes of SAT and VAT were more strongly and consistently associated with higher cardiovascular risks in women than in men [59]. These findings suggest that women who accumulate more VAT have a higher cardiovascular risk than men with more VAT.

5.3 Type II diabetes mellitus

Type II diabetes mellitus (TIIDM) is also known as non-insulin-dependent or insulin-resistant diabetes and is characterized by high blood glucose, polyuria, and polydipsia. The most common risk factors attributed to TIIDM are poor diet and lack of exercise but have also been linked to obesity. TIIDM was traditionally

been considered a disease of adulthood, but this is rapidly changing since there is an increased incidence of TIIDM in children and adolescents [60]. The common comorbidities of TIIDM include metabolic syndrome, increased adiposity, and inflammatory conditions [37].

Males and females exhibit sex-specific differences in total muscle mass and in distribution of muscle that becomes apparent in puberty. Males typically have greater total muscle mass and greater in the upper body compared to the lower body [61]. Janssen et al. performed whole body MRI in men and women 18–88 years of age, and the results of their study suggested that men had significantly higher skeletal muscle mass than women relative to total body mass (38% vs. 31%) and that the sex differences were greater in the upper body (40%) than lower body (33%) [62]. It further showed that with aging, there is an age-associated loss of muscle mass, with the greatest loss in the lower body [62].

Skeletal muscle plays an important role in determining glucose homeostasis as the muscle mass is responsible for the majority of basal and insulin-stimulated glucose uptake. In addition, impaired insulin activity at the level of the skeletal muscle is a central component to the clinical findings associated with TIIDM. The reported sex differences in muscle mass emphasize the differences of maintaining muscle during aging and could represent an important target in women who are at greater risk for sarcopenic obesity given their higher fat and lower muscle mass [63].

Studies have shown that exercise and fasting both present conditions that result in lower insulin levels with greater instances of insulin receptor binding. However, obese conditions result in greater levels of insulin with low insulin binding. A study conducted by Hotamisligil et al. suggests that TNF-a secretion by adipocytes decreases insulin-mediated glucose uptake by lowering the usage of glucose by fat and muscle tissues [64]. Insulin aids in glucose uptake in conjunction with the GLUT4 receptor. However, with the inability of insulin to properly interact with its receptor, GLUT4 is unable to take up glucose, and it continues to circulate throughout the blood [65]. The increased blood glucose and the increased inflammatory cytokines produced by the adipose tissue exacerbate TIIDM pathology.

If the levels of adipokines and free fatty acids rise, their presence will result in the recruitment of inflammatory cell types such as macrophages. When the inflammatory cells are recruited to the adipose tissue, they become activated and release additional cytokines such as TNF-alpha and IL-6 to recruit even more inflammatory cells. This results in a positive feedback loop that results in a chronic state of inflammation. Inflammation-resolving proteins such as annexin A1 are typically increased in obese patients but are inactivated by dysregulated cleavage [66]. Cleavage of annexin A1 deactivates the inflammation-resolving properties of the protein, leading the patient to maintain a chronic state of inflammation [66].

Various estrogen replacement therapy studies have shown that estrogen provides anti-inflammatory and antioxidant effects in women [67]. A meta-analysis of these studies investigated the effects of replacement therapy on women based on the age they start therapy and noted that when women began therapy within 10 years of entering the postmenopausal phase of life, estrogen provided protective anti-inflammatory and antioxidant effects [12]. When women present with TIIDM, the benefits of estrogen are also lost regardless of age of onset, and they begin to present with the same diseases that are typically more prevalent in postmenopausal women [68].

The loss of estrogen protection after TIIDM diagnosis causes the female body to be attacked more aggressively compared to men of the same age. Men diagnosed with TIIDM have significantly lower levels of testosterone compared to healthy men, while women have significantly higher levels of testosterone [69]. These data suggest that the sex hormones can regulate TIIDM severity in both men and women.

5.3.1 Chronic kidney disease in TIIDM

TIIDM diagnosis increases the risk of kidney stones and hypertension, both of which are precursors for CKD [70]. CKD is not usually diagnosed until the patient goes to the doctor for a physical, and they are diagnosed with high blood pressure, or protein is found in the urine. The Centers for Disease Control has estimated that as of 2015, 14% of the US population lives with CKD; of those that live with CKD, approximately 22% also have TIIDM.

Recent studies have shown parallels between the obesity epidemic and the onset of CKD. Obese patients with CKD are often seen with glomerular scarring, also known as glomerulosclerosis. This is now being termed obesity-related glomerulopathy due to its prevalence in obese patients [71]. Development of this condition has been related to lipid accumulation in the kidneys which may be a response to hyperfiltration if the patient also has TIIDM [71]. Under normal conditions glucose is not filtered through the glomerulus. However, if a patient has unregulated TIIDM, glucose is constantly being filtered out through the glomerulus, which becomes more permeable when blood glucose levels are high. When the glomerulus is constantly filtering glucose, the glomerular net becomes weak and more permeable to other large molecules such as proteins. This eventually leads to total dysregulation of the glomerulus and, ultimately, CKD [72]. Diabetic kidney disease is the leading cause of CKD worldwide and affects over 40% of patients diagnosed with TIIDM [73].

The overall increase in adiposity in obesity in patients with TIIDM is also correlated with an increase in kidney stone formation. Due to the increased levels of circulating adipokines released by the engorged adipocytes, these patients have an overall inflamed profile that results in higher levels of oxidative stress that can lead to the development of nephrolithiasis or kidney stones. Chronic kidney stone formation can also affect glomerular filtration rate and lead to CKD [70]. This increase in oxidative stress further upregulates inflammation in a positive feedback loop that can eventually lead to CKD and more serious pathology.

Advanced diabetes-related kidney disease is more prevalent in women than in men. However, men have a greater risk of onset. This difference may stem from how diabetes negates the protective qualities of estrogen. The effects of TIIDM on testosterone are unknown but do not appear to lead to progression of diabetes-related kidney disease. Women with TIIDM appear to have diabetic kidney disease more severely than men [74–76]. Obesity-related CKD that does not coincide with metabolic abnormalities is more prominent in men than women [77]. Estrogen may prevent kidney dysregulation in women, but these protective effects are negated in women with metabolic abnormalities.

5.4 Cancer

Approximately 14% of cancer deaths in men and 20% of cancer deaths in women can be attributed to obesity [78]. This can be related to the activation of signaling pathways in adipocytes which lead to secretion of low levels of inflammatory cytokines by the adipocytes, thereby leading to low-grade inflammatory responses throughout the body in locations where fat is most present [78]. Similarly, obesity increases endoplasmic reticulum stress resulting in oxidative stress, the unfolded protein response, and the upregulation of additional inflammatory cytokines [78]. These different inflammatory mechanisms can all contribute to the formation and progression of cancer, making obesity a deadly player in the onset of certain cancers.

The incidence of certain sex-linked cancers, such as breast cancer, may be upregulated in obese patients. In women specifically, the dysregulation of hormones that is linked with obesity can exacerbate the onset of breast cancer [79].

Non-sex-linked cancers, such as liver cancer, may also have an increased risk in relation to obesity [78]. The obesity-related development of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and NASH-related cirrhosis are also associated with an increased risk of hepatocellular carcinoma [78]. By affecting both sex-linked and non-sex-linked cancers, obesity's wide range of potential effects on tumor initiation and progression could contribute to an increased prevalence of cancer in obese patients.

A meta-analysis of cohort studies done by Larsson and Wolk found that obese individuals had an 89% increased risk of liver cancer [80]. However, the relative risk for liver cancer was significantly higher in men than in women, indicating that there may be hormone-dependent mechanisms at play [80]. Secretion of proinflammatory cytokines including IL-6, IL-8, IL-10, and IL-17 by hypertrophic adipocytes triggers an inflammatory cascade in the liver [81]. Damage induced by these inflammatory mediators can cause carcinogenesis. Further, the AMPK-TORC1 pathway that regulates autophagy is decreased by obesity and hypernutrition [81]. The decrease in the autophagy pathway causes a decrease in the clearance of damaged cellular organelles which can further induce inflammation and carcinogenesis.

Obesity may be a driving force in sex-related cancers such as prostate cancer and breast cancers in men and women. In women, obesity is related to a higher incidence of pre-menopausal triple-negative breast cancers, while ER-positive breast cancers had a higher incidence among postmenopausal women [82]. This is suggested in that breast cancer progression in pre-menopausal obese women is not affected by high amounts of systemic estrogen. However, in postmenopausal women, with normally low circulating estrogen levels, the incidence in ER-positive breast cancer increases. Additionally, the obesity associated risk with triple-negative breast cancer in postmenopausal women is inversely associated with obesity [82]. Among men, obesity and BMI are strong risk factors for male breast cancer [83]. Studies have shown that male breast cancer tumors show an increase in the estrogen and progesterone receptors [84]. The hormone aromatase, produced by the adipose tissue, plays a role in increasing estrogen levels by converting testosterone into estrogen and can therefore exacerbate breast cancer in obese men.

In summary, studies have indicated that there are sex-related differences in relation to obesity and the onset of cancer, specifically in response to breast cancers. Low-grade inflammation as a result of obesity seems to be an underlying cause of the disruption of important protective pathways, contributing to the initiation and/or progression of cancer.

5.5 Neurodegeneration

Neurodegeneration involves the gradual breakdown of the nervous system and causes anxiety, dysphoria, apathy, disinhibition, and euphoria [85]. Alzheimer's disease, (AD) the most common neurodegenerative disease and the sixth leading cause of death in the United States, is the cause of death in one in three seniors living in the United States [86]. It is estimated that 5.7 million Americans are affected by Alzheimer's, two-thirds of which are women [86]. Currently AD is the only unpreventable, untreatable disease of the top 10 leading causes of death in the United States [86]. While the cause of Alzheimer's may be unknown, research has shown strong links between neurodegeneration and obesity.

AD and other dementias occur more commonly in women than in men worldwide suggesting that there may be some sex-specific hormonal influences to the progression of the disease [87]. Although the specific hormonal influences are not known, men may have a certain ability to protect themselves against the severity of neurodegeneration, or women may simply lose their ability to do so. As awareness

increases, TIIDM is becoming recognized as a contributor to the risk of developing AD [88]. The widespread association between TIIDM and neurodegenerative diseases may eventually wind up providing a link between the two. With the expected population diagnosed with diabetes reaching 573 million within 12 years by the World Health Organization, research into the implications of diabetes and other overnutrition illness is becoming essential [89].

Neurodegeneration related to over nutrition has been shown to have profound implications on the functionality of the central nervous system and cerebral functions in particular. Recently, the IKK-beta/NF-kappaB pathway has been shown to be triggered by overnutrition, leading to inflammation of the hypothalamus and other CNS peripheral tissues [90]. This is critical because the hypothalamus is responsible for regulating functions such as energy balance as well as controlling some metabolic activities related to the sympathetic and parasympathetic nervous systems [90]. This inflammation due to overnutrition has been deemed "metabolic inflammation" [90].

A diet that is high in fat may contribute to the progression of neurodegeneration through increased fatty acid uptake. Saturated fatty acids cause activation of the immune system through Toll-like receptor 4 (TLR4), leading to the production of cytokines by astrocytes [91]. This thereby induces an inflammatory response that could lead to damage of the hypothalamus. Additionally, loss of normal function of the TLR4 increases and encourages diet-induced obesity [91]. This positive feedback loop would encourage inflammation while also sustaining the nutrient- and fat-rich environment in which it was produced. Microglia, macrophages in the brain, produce inflammasomes in diseased states such as obesity and TIIDM [91]. Therefore, any inflammation already pre-existing in the body due to obesity would only encourage self-damaging signaling cascades. These processes hijack the body's natural defense mechanisms to further the progression of neurodegeneration.

Advanced glycation end products, or AGEs, are markers of carbonyl stress due to oxidative stress, and their formation is irreversible and leads to protein deposits and amyloidosis [92]. Unnatural amyloid deposits in critical areas of the central nervous system can result in irregularities of normal functioning, and AGE formation seems to occur early in the stages of plaque formation in connection with AD [92]. AGE leads to a release of free radicals that are associated with the oxidation of sugars which eventually can lead to site-specific attacks of proteins and lipid peroxidation [92]. Additionally, when AGEs induce the expression of AGE cell surface receptors (RAGE), superoxide radicals and hydrogen peroxide are released, further contributing to cytotoxic effects on cells and inflammation [92]. The combination of these effects continues to incite an inflammatory response and furthers the progression of the neurodegenerative diseases and other neurological damages. These findings support the claim that hyperglycemia-derived AGEs constitute a crucial link between diabetes and AD [91].

Diabetes mellitus may serve as a very relevant risk factor for AD. This link may be due to the existence of insulin resistance in both patients affected by TIIDM and in neural cells [93]. Insulin receptors activate receptor tyrosine kinases which in turn phosphorylate insulin receptor subtypes 1 and 2 [93]. The interaction of these receptors with Src domains allows for several protective processes to occur and promote cellular division and longevity of healthy cells [93]. Cells that are deficient in this receptor, or that cannot express sufficient amounts, are subsequently at risk for diminished functioning capabilities. Furthermore, insulin specifically binds to the respective receptors to initiate different functions, so the expression of both receptors is vital to cellular functioning [93]. In the brain, the highest levels of insulin are found in the hypothalamus, temporal lobe, and cerebellum [93]. A lack of the protecting effects of insulin may explain why the hypothalamus is classically inflamed in conditions of obesity.

Obesity-associated low-grade inflammation seems to be an underlying cause in the progression of neurodegenerative diseases, specifically AD. While there seem to be sex-related differences in the relationship between neurodegeneration and obesity, more research is needed to identify what the exact cause is. Nevertheless, the correlation between neurodegeneration, TIIDM, and obesity is apparent, and further research is needed to elucidate this mechanism.

5.6 Infertility

Infertility is defined as the inability of a couple to conceive after 12 months or more of regular, unprotected sex [94]. There can be many causes of infertility, but an emerging comorbidity and risk factor is obesity. Obesity can affect reproduction and development by altering sex hormones, sex cells, and different genes within the sex cells. These alterations can be found in both men and women; however, the effects differ slightly. Both sexes exhibit an increase of the androgen sex hormone [95, 96]. Obese men and women are also shown to produce less sex cells overall [97]. A 2015 epidemiological study found that over 100 genes that were related to infertility were also related to obesity [95, 96]. Furthermore, genes that support sex cell maturation and function have been shown to be altered with an increase in adiposity [98]. Maintaining a healthy body weight can help normalize these factors of reproduction, while obesity can cause reproductive alterations that can result in infertility.

5.6.1 Males

Infertility in males is linked to decreased viable sperm count, sperm motility, or supporting sex hormones. When compared to men with a normal body mass index (BMI) of 20–25 kg/m^2, obese men with a BMI greater than 25 kg/m^2 showed a decrease in concentration of the number of sperm per milliliter of ejaculatory fluid, a decrease in total sperm count in millions, and a decrease in healthy sperm cells [97]. Successful conception rates have been directly related to sperm counts; greater sperm counts correlate to an increased chance of conception, and in addition to sperm count, obesity-induced epigenetic modifications play a role in sperm-egg interaction [97]. Increased obesity-induced DNA methylation and decreased DNA acetylation affect sperm cell gene expression [99]. This change can inhibit a successful fertilization by altering embryogenesis, and this can lead to a failed pregnancy or problems in embryo development.

In males, onset of obesity correlates with an increase in estrogen and a decrease in supporting sex hormones such as testosterone, sex hormone-binding globulin (SHBG), and inhibin B [97]. SHBG is mainly produced in the liver and primarily functions by binding to and transporting sex steroids throughout the blood. Decreased SHBG protein levels have been linked to metabolic and endocrine disorders and obesity [100]. Obesity has been correlated with low secretion levels of luteinizing hormone (LH) from the pituitary gland, which induces testosterone release from the Leydig cells. In a healthy male, after testosterone secretion, a majority of the steroid would bind to SHBG and then travel to various androgen receptors throughout the male body, with small levels being converted to estrogen via aromatase. However, obese patients tend to have a greater aromatase activity and therefore have higher levels of estrogen than nonobese men [99]. An increase in metabolism of free testosterone to estrogen can lead to decreased testicular sensitivity to LH, further leading to high estrogen and low testosterone levels [99]. This creates a negative feedback loop, ultimately leading to a decrease in sperm production.

Inhibin B is a glycoprotein produced by Sertoli cells that aids in regulating follicle-stimulating hormone (FSH) in a negative feedback manner [101]. When

spermatogenesis appears to be elevated based on activity of the hypothalamic-pituitary-gonadal hormone (HPG), this indicates a high sperm count due to FSH secretions. Inhibin B will regulate FSH levels based on HPG status which modulates sperm concentration. An inhibin B study found that a negative correlation between sperm count and inhibin B was revealed [101]. Inhibin B activity is high when sperm count is concentrated; infertile men often have very low levels of inhibin B; this relationship indicates further exacerbation of infertility and low sperm count. Decreased gonadal function in obese men has been characterized by lower levels of inhibin B even though FSH levels remain similar before and after weight loss [102]. Therefore, while obese males have similar levels of FSH to nonobese males, the high aromatase activity converts much of the testosterone to estrogen, thereby inhibiting spermatogenesis and decreasing fertility [103].

Lastly, in healthy males, the scrotum usually is about 2–3°C lower than body temperature, which is essential for sperm storage, health, and motility [104]. Obesity can also result in increased scrotum temperatures which can lead to infertility [104]. The changes associated with obesity-induced infertility can be circumvented by weight loss [104]. Staying healthy and maintaining a moderate BMI can help regulate hormone and sex cell secretions and promote fertility.

5.6.2 Females

Obesity in females can lead to infertility by decreasing oocyte quality, altering ovulation, and affecting developmental factors. The mitochondria and mitochondrial oxidative phosphorylation are essential to oocyte maturation, fertilization, and implantation [105]. It has been shown that mice lacking the mitochondrial replication protein, TFAM, are embryonic lethal and reduced levels of TFAM cause decreased fertility [106]. The effects of high-fat diet (HFD) on obesity are summarized in Grindler et al. but briefly show that HFD-induced obesity alters mitochondrial function and mitochondrial membrane potential, increases reactive oxygen species, and decreases mitochondrial DNA copy number in oocytes which indicates damaged and unhealthy oocytes [105]. Regular diets with less fat would minimize mitochondrial dysfunction and oxidative damage to oocytes and keep them viable.

Menstrual abnormalities contributing to infertility like anovulation are seen in obese women [107]. SAT plays a role in regulating anovulation, whereas VAT plays more of a role in proinflammatory secretions [108]. Regulating fat intake can improve chances of conception by regulating menstrual cycles and oocyte development. Further, the proinflammatory secretions from VAT create a positive feedback loop causing more inflammation and more ovulation complications. The changes in ovulation and the increased levels of inflammatory cytokines exacerbate infertility in females.

Regulation of the follicular environment is necessary for oocyte development, and obesity changes the follicular environment and consequently the oocyte gene expression which contribute to infertility [109]. Leptin is typically elevated in obese patients and can cause negative changes to the follicular environment. Interestingly, women with higher BMI have higher levels of lactate, triglycerides, and CRP and decreased levels of SHGB in their follicular fluid, compared to normal-weight women, which can be linked to decreased oocyte viability and an inhospitable environment for oocyte development [109]. In addition, the same decrease in SHBG seen in obese men was seen in obese women [109]. This decrease in SHBG expression would lead to decreased transport of estrogen and thereby decreased oocyte development. This suggests that secretions from adipose tissues could be contributing to decreased oocyte function. Further, when oocytes were extracted from women of BMIs considered normal, overweight, and obese, fewer oocytes

were obtained from the women in the obese category with a BMI of greater than 30 kg/m^2 [109]. Taken together this data indicates that obesity impairs oocyte development.

The increase in C-reactive protein suggests that systemic inflammation can also affect fertility and oocyte development [109]. High amounts of inflammatory secretions such as C-reactive protein seen in obese women contribute to decreased fertility. Obesity-induced inflammation presents damaging effects to oocytes and contributes to infertility. Obesity decreases chances of healthy oocyte fertilization and implantation. Couples will have a better chance at conception and successful pregnancy if a healthy weight is maintained.

5.7 Stress

Obesity and stress cause a vicious positive feedback loop to cause more obesity and stress. Outside stressors activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. When these systems are dysregulated by continuous stress, the hyperactivity causes health issues, such as obesity [110]. Under normal conditions, the HPA axis is needed to maintain energy and metabolic homeostasis through modulating hormones such as insulin and leptin [111]. When activated, the sympathetic nervous system will cause secretion of epinephrine and norepinephrine from the adrenal gland, and the HPA axis will release cortisol. Negative feedback mechanisms inhibit the HPA axis from continuously secreting cortisol and maintaining alterations in metabolism [112]. Homeostatic fluctuation of the HPA axis controls metabolism; however, stress and inflammation alter this feedback loop and contribute to metabolic dysfunction.

Obesity-induced inflammation has also been correlated with an increase in the HPA axis function. Cortisol can increase leptin levels and inhibit leptin from suppressing appetite, or cortisol can induce neuropeptide Y release, which stimulates fat growth [110]. Therefore, cortisol can increase fat deposition. The origin of cortisol, from stress or normal homeostatic activation, and the obesity status play a role in fat deposition. For example, stress-induced increases in cortisol levels cause women to gain more weight compared to non-stressed women with the same cortisol levels. Further, elevated cortisol levels in overweight women cause increased weight gain at a faster pace than women with average weight and similar elevated cortisol levels [110]. The correlation between cortisol and weight gain in men appears to be related more to weight gain than to increases in cortisol levels, and the increased cortisol production seen in men could be further stimulated by the inflammatory cytokines secreted in fat tissues [110]. Together, this data suggests gender differences in cortisol-induced adiposity.

Stress can affect choice of food intake differently in males and females by modulating appetite. While most individuals were seen to eat less in high stress, individuals were seen to eat more in continuous low or moderate stress levels [113]. This suggests that prolonged moderate stress could contribute more to obesity than high stress in a shorter time period. Not only does stress increase appetite for some people, but it also affects food choice. Individuals under stress were seen to increase the intake of higher-calorie "comfort foods" in replacement of vegetables [111]. These findings support the role of stress-induced weight gain in chronically stressed people.

Ideas of self-image, ideal weight, or body shape also lead to increased stress. The ideas of normal or desired body image are found everywhere and are often unrealistic and idealized. The role of weight-based stigmas and how they differ in males and females offer inconclusive results [114]. In a recent study by Sattler et al., weight-based stigmas in obese population caused weight gain and a decreased

desire to exercise in females more than males [114]. Females with weight-associated stigmas had less motivation to participate in physical activities, while males had more motivation to exercise [114]. These stigmas can cause increases in stress levels and cortisol release and may actually have a negative impact on exercise and weight loss in obese patients. The idea that this weight stigma differentially affects males and females is important to understand, in order to effectively motivate overweight and obese males and females to exercise and to lose weight. This data suggests that the stress of ideal body image can also negatively affect stress-induced adiposity.

Stress and obesity combined contribute to fat growth, changes in appetite, and additional stress. The negative self-image, depression, or anxiety that obese people have provides the stress for prolonged HPA axis activation and increased adiposity.

6. Conclusion

Obesity plagues approximately 70% of US adults. Obese adipose tissue is responsible for releasing proinflammatory cytokines throughout the body as well as dysregulating glucose-regulating hormones. Chronic obese adiposity puts the body in a state of chronic inflammation which leads to numerous diseases including CVD, TIIDM, MetS, cancer, neurodegeneration, and infertility (**Figure 2**). Sex differences play a role in regulating the prevalence of disease, causing sexual dimorphism in diseases and disease pathogenesis in men than women. The role of the sex hormones, estrogen, and testosterone should be further explored in order to most effectively treat obese patients and their numerous pathophysiologies.

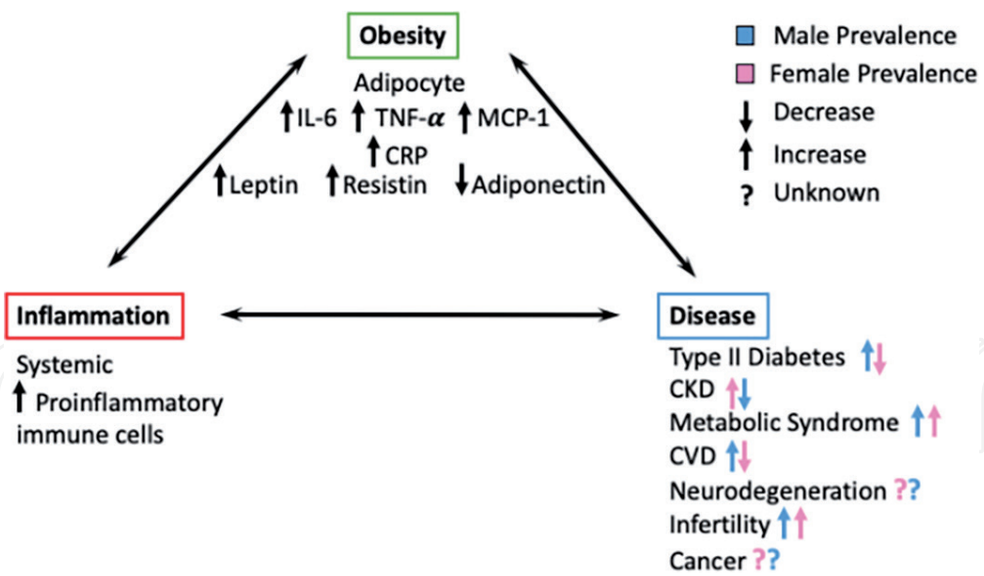

Figure 2.
The relationship between obesity, inflammation, and disease. Obesity, inflammation, and chronic diseases cause a vicious cycle, each exacerbating the other. Inflammatory cytokines and adipokines are produced systemically and by adipocytes, respectively, and play a role in exacerbating disease states. Prevalence of disease caused by inflammation and obesity varies between men and women, and sex differences may be due to the proposed protective nature of the primary female sex hormone, estrogen.

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Author details

Sari Terrazas[1], Lauren Brashear[1], Anna-Katherine Escoto[1], Shannon Lynch[1], Dylan Slaughter[1], Neena Xavier[2], Norman Robert Estes II[1] and Samantha Giordano-Mooga[1*]

1 Biomedical Sciences Program, Department of Clinical and Diagnostic Sciences, University of Alabama at Birmingham, Birmingham, Alabama, USA

2 Physician's Assistant Program, Department of Clinical and Diagnostic Sciences, University of Alabama at Birmingham, Birmingham, Alabama, USA

*Address all correspondence to: sgiordan@uab.edu

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