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A Narrative Review of Obesity and Its Associated Complications in Iranian Women

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Abstract

Context: Obesity is a major public health problem worldwide. This review aimed at providing an updated overview of obesity in Iranian women and its associated complications.

Evidence Acquisition: In this narrative review study, related systematic reviews or meta-analysis studies of high ranking journals conducted from 2000 to 2016 were searched in the PubMed, Medline, and Scopus with the following keywords: "women OR female" AND "weight OR overweight OR obesity", "risk factors OR complications", "reproduction OR cancer OR cardiovascular disease OR diabetes OR gestational diabetes OR maternal obesity OR fertility OR pregnancy OR polycystic ovary syndrome" OR management.

Results: In Iran, women have shown a constantly higher risk of obesity compared to men. After a 9- year follow-up, the age-standardized incidence rate (95% CI) of diabetes was 10.1 (7.24 - 13.9) in women. The increases in overweight and obesity in menopausal women have an important role in endometrial, colon, and breast cancer. Obesity increases the risk of endometrial cancer 2.4 to 4.5 folds compared to the normal weight women. Maternal obesity increases the risk of gestational hypertension 4.5 to 8.7 times compared to normal weight women. An increasing number of obese women becoming pregnant is associated with short- and long-term maternal and child outcomes. The prevalence of childhood obesity in children of obese women aged 3 to 5 years increases up to 25%; and these children have an almost 6- fold chance of being obese in young adulthood. Weight reduction of obese women is accompanied with lower incidence of obesity complications. The most effective interventions are multiple behavioral management activities.

Conclusions: Considering the large population of young people in Iran and the lack of any effective preventive policy, the burden of obesity and its associated outcomes will be problematic in the near future.

Keywords: Women, Obesity, Reproduction, Cancer, Cardiovascular Disease

1. Context

1.1. The Health Outcome and Economic Cost of Obesity

The high rate of increase in the prevalence of obesity and its related disorders in the recent decades has proposed it as a serious health concern worldwide (1). It is approximately estimated that 1 in each 3 women is affected by obesity (2). The high prevalence of obesity in the United States leads to considerable increase in morbidity and mortality and health care costs. Obesity is often due to the combination of personal and social characteristics, but is often viewed as a personal identity rather than a medical condition, hence, this makes a distinction towards obese individuals and decreases the likelihood of an effective intervention (3).

1.2. The Prevalence of Obesity in the World

Between 1980 and 2013, the rate of overweight and obesity increased by 27.5% (857 million in 1980 to 2.1 billion in 2013) in the adult population of the world. In particular, the prevalence of excess body weight among women worldwide in 1980 to 2013 has been increased by 8.2% (from 29.8% to 38.0%). Interestingly, the patterns of increasing prevalence of overweight in developing countries differ from developed countries. In developed countries, the proportion of overweight and obese men was higher than women, while in developing countries the prevalence of overweight and obesity was higher in women than in men (4).

1.3. The Prevalence of Obesity in Iran

Based on a recent systematic review conducted by Jafari-Adli et al., it was indicated that in line with previous reports from different regions of the world, there is an alarming augment for overweight and obesity prevalence among all ages and the 2 sexes in the Iranian population (1). Results from a previous investigation on 10 368 individuals in Tehran Lipid and Glucose study (TLGS)

demonstrated that the raw prevalence of obesity and abdominal obesity increased from 23.1% and 47.9% in 1999 to 34.1% and 71.1% in 2011, respectively (5). In addition, it was shown that a sedentary lifestyle is prevalent in Iranian population, which is a well-documented risk factor for developing obesity (6). These results are consistent with the systematic review study and indicated that the trends of obesity is rapidly rising in both sexes and all social levels in population, which calls for urgent preventive public health strategies to educate and empower the community members, specially mothers and housewives for modifying obesity in families (1, 5). The newest report from the TLGS revealed that after a median of 8-year follow up, the incidence of obesity (body mass index = BMI $\geq$ 30) was 31.3% (CI: 29.9% - 32.7%) among the non-obese population, which was 38.1% (CI: 36.2% - 40.1%) in women and 23.4% (CI: 21.6% - 25.3%) in men. The highest incidence rates were found in women and men aged 40 and 20 years, respectively. Furthermore, it was demonstrated that individuals with higher BMI or waist circumference (WC), lower levels of schooling, and metabolic syndrome, had higher risk for developing obesity (7). The global and regional reports on the prevalence of overweight and obesity in children and adults during 1980 to 2013, have demonstrated that age-standardized estimates of the prevalence of overweight and obesity together and obesity exclusively for women aged $\geq$ 20 years had the highest rate between all different sex and age groups in Iran (4). Thus, the present review attempted to provide an updated overview of obesity in Iranian women and its associated complications.

2. Evidence Acquisition

In this narrative review study, related systematic reviews or meta-analysis studies of high ranking journals with more citation about the prevalence of obesity and its complications in women conducted from 2000 to 2016 were searched in the PubMed, Medline, and Scopus with the following keywords: "women OR female" AND "weight OR overweight OR obesity", "risk factors OR complications", "reproduction OR cancer OR cardiovascular disease OR diabetes OR gestational diabetes OR maternal obesity OR fertility OR pregnancy OR polycystic ovary syndrome" OR management.

2.1. Definition

Excessive and abnormal fat accumulation in adipose tissue can lead to overweight and consequently obesity. Currently, the most practical indicator for evaluating excess body weight is the BMI and WC (1, 8).

BMI is calculated as weight (kg)/ height squared (m^2). Based on the international classification of adult underweight, overweight and obesity, and the normal range of BMI is defined as 18.5 to 24.9 and 25.0 to 29.9, indicating preobese or overweight individuals, and $\geq$ 30.0 refers to obese individuals which was divided in three subclasses of obese class I (30.0 - 34.9), obese class II (35.0 - 39.9), and obese class III ($\geq$ 40.0) (9, 10). Given the reports of the Iranian national committee of obesity, WC $\geq$ 90 cm in both sexes indicates the population who are at risk for cardiovascular disease (CVD) risk factors and requires life style modification as well. WC of $\geq$ 95 cm in both sexes specifies high-risk individuals for CVD events and requires instant preventive interventions (11).

According to world health organization (WHO) criteria, overweight and general obesity were defined as BMI 25 - 30 and $\geq$ 30 kg/m^2, respectively, central obesity as WC $\geq$ 102 cm in men and $\geq$ 88 cm in women, waist to hip ratio (WHR) as $\geq$ 0.95 in men and $\geq$ 0.8 in women.

3. Results

3.1. Some Risk Factors of Obesity and Overall Complications

A variety of heredity and early life risk factors (eg, having obese parents and birth weight), sociocultural, economic, environmental, and behavioral factors, as well as urbanization, and modifiable lifestyle risk factors such as low level of physical activity, short sleep duration, and unhealthy dietary habits are involved in developing obesity (12-20). The complex impact of genetic and environmental factors may affect individuals' susceptibility to being obese. It has been well established that the obese state is contributed to increased risks of developing many chronic diseases such as Type 2 diabetes (T2DM), cardiovascular disease, hypertension, arthritis, and some types of cancers such as esophagus, breast, endometrium, colorectal, and gallbladder. Previous studies have demonstrated that dietary intakes play an important role in the development of obesity (21). For instance, vitamin D deficiency can significantly increase the risk of obesity particularly in women (22, 23).

3.2. Obesity and Diabetes in Women

Accumulating evidence from epidemiological studies in different population worldwide indicates that overweight and obesity are the most known risk factors for developing diabetes. Interestingly, the effects of overweight and obesity on the risk of T2DM are independent of each other. In addition, longer duration of being overweight or obese is positively associated with elevated risk of diabetes (24-28).

The recent analysis of the TLGS showed that after 9 years of follow-up, the age-standardized incidence rate (95% CI) of diabetes was 10.1 (7.24 - 13.9) in women and 9.36 (5.84 - 14.92) in men. Moreover, it was found that general adiposity as indicated by BMI and lower education level in men and central adiposity, which was described by WHR and WC in women, were related to incident diabetes (29). Furthermore, in another recent analysis of this prospective study, it was demonstrated that WC ($\geq$ 102 cm in men and $\geq$ 88 cm in women) is the best indicator for identifying individuals $\geq$ 60 years with diabetes, whereas obesity (BMI $\geq$ 30) and WHR ($\geq$ 0.95 in men and $\geq$ 0.8 in women) are two useful anthropometric measurements in identifying younger diabetic individuals (< 60 years) (30).

The strong association between obesity and metabolic syndrome, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT), insulin resistance, hyperinsulinemia, and adiposity has been well established. Both subcutaneous and visceral fat contribute to insulin resistance, eventually leading to T2DM (3, 26). Therefore, modification of lifestyle (ie, improving eating habits and increasing physical activity) is necessary for both sustainable weight reduction and diabetes prevention (3).

3.3. Obesity and Cardiovascular Diseases

The severity of abdominal obesity, especially in women, is one of the key factors in the pathogenesis of obesity-related disorders including diabetes, metabolic syndrome, and CVD (31-37). Therefore, to reduce the risk of cardiovascular events, central obesity should be prevented or stopped (38).

The certain link between obesity and elevated risk of CVD clearly indicates that there is a chronic inflammatory state as the result of complex factors including visceral obesity and excess fat storage, insulin resistance, an atherogenic dyslipidemia, and hypertension (39).

Many people, in particular middle-aged women and men, are affected by obesity and its related complications. Females (specifically after menopause) are at higher risk for developing visceral obesity because of the lack of endogenous ovarian hormone production. Estrogen exerts its effects through 2 nuclear estrogen receptors (ERs): α and β. This hormone and its receptors play an important role in regulating body weight and insulin sensitivity not only in women but also in men (37).

3.4. The Impact of Obesity on Females' Health

In an obesogenic environment, women are more affected by obesity and its complications than men. Obesity is more prevalent in women than men, especially in developing countries. Thus, due to the importance and positive effects of women's health on families and on babies during pregnancy, the increasing rate of obesity in female gender should be considered as an urgent issue (4, 8, 12).

Therefore, because of the critical role of women in families, the societal consequences of higher prevalence of obesity among women, compared to men, may lead to worse irreversible effects. Having excess body weight can result in adverse outcomes in women's health during all stages of life. In younger ages it has psychosocial complications and during the later years, women's reproductive system may be highly affected by excess body fat (8, 40).

In general, the psychosocial, economical, and biological consequences of obesity are more apparent in women than in men. Furthermore, obesity in women poses intergenerational impacts due to the mother-to-child transmission issue during pregnancy, which means being an overweight or obese mother may transmit the risk of obesity and its health related comorbidities to the children (8, 41).

3.5. Obesity and Female Reproductive Fertility

Based on our present knowledge, there is strong association between high BMI and lower pregnancy and live-birth prevalence as well as higher miscarriage rate. It has been proposed that some coexisting factors including age and polycystic ovary syndrome status may play a significant role in the pathogenesis of these adverse effects. In addition, most of obese women undergoing assisted reproductive technologies (ART) exert unpleasing ovarian activation characteristics such as fewer selected follicles and lower number of recovered oocytes. The mechanisms underlying these adverse outcomes, whether ovarian or endometrial, are not fully understood yet (42).

Furthermore, obese women are more subjected to elevated risk of certain complications during pregnancy including gestational hypertension, periodontitis, diabetes mellitus, preeclampsia, thromboembolic diseases as well as adverse breastfeeding outcomes in addition to adverse effects on fetal and infant growth and development such as fetal macrosomia, late intrauterine fetal and stillbirth death, early neonatal death, and postpartum anemia (43-46).

Moreover, maternal obesity may have a profound impact on offspring health status by creating an unsuitable genetic, hormonal, and biochemical changes in the fetus or the embryo development, and consequently, influences fetal growth and organ development. Neonates of obese mothers have an elevated risk of perinatal mortality because of more susceptibility to certain disorders such as fetal demise, congenital anomalies, and disrupted growth patterns. In addition, these children are at higher increased risk of being affected by chronic disease including cardiovascular disease, metabolic syndrome, T2DM, os-

teoporosis, cancer, neurodevelopmental delay, and aging (44, 47, 48). Thus, the impact of maternal obesity extends beyond neonatal and perinatal period to childhood, increased risk of health complications in adolescence, and adulthood with the potential to result in an 'intergenerational cycle' that could have adverse impacts on a number of generations (48, 49). For example, based on the studies in Iranian families, a significant mother-daughter correlation of central obesity has been found which may demonstrate the important role of the mother's health on obesity prevention of their offspring's, especially in high-risk families (50). Currently, there are strong recommendations for obese pregnant women, which imply the maximum weight gain during the whole pregnancy to be 5 to 9 kg. Thus, the old belief stating that a pregnant woman must "eat for 2" is inappropriate. Therefore, it seems essential to design lifestyle interventions aimed at reducing gestational weight gaisuch as improving eating habits and increasing physical activity levels, which may benefit the mother, her children, and the next generations. For example, currently, supplementation with folic acid and vitamin D are recommended for preventing malformation and fetal neural tube defects in addition to maternal vitamin D deficiency, respectively (51).

3.6. Obesity and Pregnancy Outcomes

3.6.1. Gestational Diabetes and Maternal Obesity

Recently, the high proportions of overweight or obese women are in reproductive ages. Gestational diabetes mellitus (GDM) is associated with maternal obesity which consequently induces long-term adverse outcomes in the offspring and subsequent generations. In addition, GDM plays an important role in the raising global burden of diabetes and CVD (52).

The process by which maternal obesity and excess BMI level can lead to gestational diabetes is similar to that of nonpregnancy diabetes mellitus. Adipocytes release various hormones and adipokines which interfere with insulin function and finally lead to insulin resistance and hyperglycemia. Mothers with gestational diabetes are at a higher risk of pregnancy-related hypertension, cesarean delivery, developing T2DM in the future, and having obese children (53). The risk of adverse outcomes of maternal excess body fat increases with increasing BMI level and in women with a BMI of 40 reaches to the highest morbidity rate of mothers and her offspring. This is especially important in the prevention of developing GDM in overweight and obese mothers. Therefore, both reducing excess body weight to normal levels and lowering the weight and BMI within the obese range appear to be highly important in reducing adverse pregnancy outcomes (54).

Obesity is listed as a main risk factor for pre-eclampsia and gestational hypertension. Two reviews showed that maternal obesity increased the risk of pre-eclampsia 3 to 10 times and gestational hypertension 4.5 to 8.7 times compared to normal-weight women. The retrospective study on women admitted to the United States hospitals, 2 cohorts in Canada and Scotland observed a positive association between obesity and pre-eclampsia and gestational hypertension. The other factors including insulin resistance, genetics, immunology, as well as an unhealthy diet, and lack of physical activity increased the risk of pre-eclampsia (55).

3.6.2. Polycystic Ovary Syndrome (PCOS)

PCOS, also known as hyperandrogenic anovulation, is a common endocrine system disorder which affects women at reproductive age. The etiology of this disorder has not been well understood. The hyperandrogenic anovulation state can influence the body fat distribution, insulin resistance, menstrual irregularity, infertility, hirsutism, and/or acne (36). According to extensive research, obesity and metabolic syndrome in women with PCOS is much more prevalent than in the general population. Obesity, increasing body weight, body fat accumulation, and insulin resistance elevate the risk of developing PCOS and exacerbating its clinical symptoms through complex and pathways, influencing androgenicity in women affected by the disease. Excess body weight and body fat distribution effects secretion, transport, metabolism, and action of androgens. Thus, obesity in women may also pose a higher risk of developing hyperandrogenism as a result of a decrease in the synthesis of sex hormone-binding globulin (SHBG) and consequently increased levels of free testosterone (56, 57). Weight gain in these patients increases the severity of the disease, and in contrast, weight loss has a positive effect on androgenicity in women with PCOS. Ultimately, the caregivers should pay special attention to the issue of reducing weight and improving eating habits in the treatment process of this disease (57).

3.7. Infertility

Obesity-induced infertility in women is one of the most important complications of excess body fat that is not addressed well. The regulation of oocyte growth and its secretion time or ovulation, in addition to its ability for fertilization and converting to an embryo, is greatly affected by maternal health and nutritional status. There are extensive studies which demonstrate that obesity in women may interfere with the ovary mechanisms of actions and the formation of embryo which finally result in reducing the potential of women's reproductive system. Thus, a high BMI lowers a woman's chance of being pregnant even with a

normal ovulation status. Moreover, obese women are less likely to respond to the gonadotropin hormone therapy. Obesity-induced alterations in mitochondria and the endoplasmic reticulum, in addition to the low grade inflammatory state, elevated the levels of proinflammatory cytokines including CRP, which presents in the ovary as a result of higher levels of LOX-1 and oxidative stress state in response to higher lipid content and lipotoxicity (58).

Furthermore, there are obesity-induced disturbances in reproductive hormones and ovulatory function in obese women which may be considered as consequences of chronic energy imbalance. Thus, reducing total energy intake through a weight loss program as well as being physically active to increase energy expenditure eventually lead to improve energy balance and enhance reproductive function and fertility in obese female (59).

3.8. Obesity and Cancer

Severe obesity can substantially pose a higher risk of developing certain types of cancers, promoting its progression and recurrence, as well as reducing its survival through different mechanisms including increased fat mass and lipotoxicity, inflammation, hyperinsulinemia, and insulin resistance. Thus, reducing the obesity-induced inflammatory response is one of the proposed approaches for chemoprevention (60-62).

According to extensive evidence, the first linkage between obesity and cancer is the inflammatory state which exists in obesity and obesity-induced chronic disease that consequently may lead to increased aromatase expression and notably elevated production of PGE2 both in the adipose tissue and in the tumor cells. The second linkage is the role of obesity in the disturbed regulation of estrogen biosynthesis in adipose tissue that has been proposed as an imperative risk factor for the etiology of certain types of cancers in women including estrogen-dependent cancers such as breast cancer and endometrial cancer (62).

3.8.1. Breast Cancer

Obesity and higher body fat are well-known risk factors for developing female breast cancer regardless of whether being in the menopausal period or not through different mechanisms which are discussed in the following (63-68):

First, obesity induced dysregulated metabolism as a consequence of changes in energy status, endocrine function, as well as internal changes in cell state.

Second, adverse effects of hyperinsulinemia and insulin-like growth factor-I (IGF-I) on cell proliferation in breast cancer in addition to adipose aromatase activity and estrogen production, elevated secretion, and bioavailability of extraglandular estrogen.

Third, alteration in the levels of pro- and anti-inflammatory adipokines and prostaglandins, especially adiponectin and prostaglandin E2 that is observed in obesity, may also lead to elevated aromatase expression and increase tumor cell proliferation as well as tumor-related angiogenesis (63-67).

Fourth, obesity is associated with negative tumors of estrogen and progesterone receptors in female breast cancer.

Based on the results of extensive researches, higher BMI in women with breast cancer has been proposed as a predictor of development, severity, and poor prognosis after diagnosis. Thus, utilization of therapeutic approaches to treat obesity diabetes can eventually lead to decreased risk of developing breast cancer (63-68).

3.8.2. Ovarian Cancer

The ovarian cancer is responsible for a high number of deaths. Obesity and excess body fat play a vital role in increasing the susceptibility of individuals to develop ovarian cancer. The most known mechanisms proposed in the literature are elevated secretions of adipose tissue adipokines such as Leptin. It is well known that obese people have higher levels of leptin hormones due to leptin resistance state. This hormone elevates proliferation of cell and restrains apoptosis. Moreover, an endogenous estrogen, which is released by adipose tissue, elevates cell proliferation of epithelial ovarian cells. Additionally, hyperinsulinemia results in higher secretion of ovarian estrogen, which eventually leads to increased risk of ovarian cancer (69). Based on the results of a meta-analysis, being overweight or obese at early adulthood increased the risk of death from ovarian cancer (70).

3.8.3. Endometrial Cancer

Recent evidences highlighted the increasing rate of endometrial cancer. Obesity is an important risk factor for endometrial cancer in premenopausal and younger women. Obesity increases the risk of endometrial cancer 2.4 to 4.5 folds compared to normal weight women even after adjustment for the confounding factors. Obesity has been associated with alterations in hormonal and metabolic factors; in obese individuals excess adipose tissue produces estrogen, which stimulates endometrial proliferation, leading to increased risk of endometrial hyperplasia and endometrial cancer (71, 72). A 20% to 30% decrease in endometrial cancer was reported in women with moderate or high intensity exercise compared to low or non-exercisers. In addition, case-control studies showed that the Mediterranean diet might be associated with decreased risk of endometrial cancer. In contrast, high

Box 1. Interventions to Reduce Adverse Outcomes of Obesity in Pregnancy

I. Achieving a healthy weight before, during, and after pregnancy	
Interventions during the inter-conception period: achieving healthy weight prior to a subsequent pregnancy	
During pregnancy, focusing on the proper amount of weight gain based on pre-pregnancy weight status[a]	
Specific dietary interventions based on standard dietary guidelines and under the supervision and consultant of a dietitian	
II. Steps of Intervention	
Assessment	Measuring BMI and waist circumference, history of nutritional diaries, habits and physical activity
	Assessing excess adiposity
	A brief behavioral assessment in addition to the history of using weight loss programs
	Driving limits and barriers for achievement or failing of weight loss programs
	Diagnose eating disorder complication
	Determining the patient's reasoning for following weight loss programs
Setting weight loss goals	Diminishing weight and maintaining the desirable body weight over the long term
	Loss of ~ 500 - 1000 kcal of daily energy
	A realistic goal is 10% within 6 months[b]
Manage using the long-term, multimodal strategy	Nutrition therapy
	Increased physical activity
	Modifying behaviors
	Self-help method
Maintenance of weight loss over the long-term	Self-monitoring behaviors
	Good dietary habits
	Physically active lifestyle
Dietary supplements can be added to weight loss program	
Medications can be used only as part of a long-term weight loss programs	
Surgery is recommended for obese individuals with BMI $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with serious comorbidities	

[a] Weight loss during pregnancy is not recommended.
[b] The realistic goal for weight loss is 10% within 6 months; however, more patients wish to lose at least 30% of their body weight.

glycemic load diets increased endometrial cancer up to 20% (73).

3.9. Obesity Management

Reducing the risk of obesity-induced complications, in addition to lowering excess body weight as well as its long term control along with behavioral therapy of the obese patients, are the most important aims and approaches to combat obesity. In general, in a realistic weight loss program, a ~ 500 - 1000 kcal decrease in daily energy intake may be targeted to reducing 10% of body weight during 6 months, which is in contrast to the most of the patients willing to lose at least 30% of their body weight (2, 74). In nutritional management of obesity, the dietitian should assess the patient's BMI and waist circumference, and collect a full nutritional and physical activity history, and the patient's past attempts for weight loss (Box 1) (2, 75).

Moreover, to prevent obesity-induced adverse birth outcomes, greater attention should be given to the pathophysiological alterations, which occurred by obesity, as well as the psychosocial and environmental context, which has led to maternal obesity and overweight (45).

Behavioral changing approaches such as educating community members to be more physically active and adopt healthier dietary habits with or without significant weight loss can provide a unique encouraging opportunity for the health care provider and the obese patient to successfully manage obesity and its related comorbidities (76).

Preventing obesity starts from breastfeeding. Breastfeeding leaves short-term positive effects on both maternal health status and the health status of the offspring all over her/his life. The more protection from excess body weight is achieved by increasing the duration of breastfeeding (77).

4. Conclusions

Taken together, considering the large population of young people in Iran and the lack of any effective preventive policy, the burden of obesity and its associated outcomes will be problematic in the near future. Due to the well-established associations of maternal obesity with adverse lifelong outcomes of the offspring, it seems clear that maternal weight-reduction interventions eventually lead to beneficial health related outcomes in children all over their lives. Thus, considering the goal of combating the vicious circle of intergenerational obesity, effective intervention programs are needed to prevent maternal obesity by improving individual behavior, modifying the living environment, enhancing individual's dietary habits, medical therapy, and increasing physical activity.

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