Dyslipidemia in women, a current overview based on cardiovascular risk

Dislipidemia en la mujer, una revisión actual basada en el riesgo cardiovascular

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Right now, the main mortality cause in women is directly associated with cardiovascular (CV) disease. Women are currently exposed to traditional risk factors such as; hypertension, dyslipidemia, smoking, sedentarism, overweight, obesity and glucose metabolism disorders. On the other hand, women are also exposed to other unique gender risk factors such as, polycystic ovaries syndrome, high risk pregnancies, immunological diseases and hormonal disorders, all of them appearing mainly in the peri-menopause or menopause stages, resulting in a vulnerable population to suffers CV outcomes as microvascular angina, occlusive disease, coronary spasm, spontaneous coronary dissection, acute ischemic syndrome, Takotsubo disease, among others, placing women into an individualized and specialized consideration for diagnosis and treatment.

The main lipid metabolism disorders in our population, are accompanied by a lipidic profile known as the lipidic triad. This complex consists in; low concentration of cholesterol linked to high-density lipoproteins (HDL-c), hypertriglyceridemia (HTG), both directly related to the body mass index, and high cholesterol linked to low-density lipoproteins (LDL-c), whose particles undergo morphological modification (small and dense), which increases their atherogenic power.

In Mexico, CV disease represents the main mortality and morbidity cause in people > 70 years old. The data gathered by the ENSANUT survey (National Chronic Disease and National Health surveys), reveals that 32.7% of the population suffers cholesterol (CHOL) metabolism and triglycerides (TG) disorders (2018). Furthermore, when the survey was analyzed by gender, the percentage in women was 34.8% compared to 30.3% in men. Apart from dyslipidemia there are other highly relevant risk factors to take into account such as hypertension, type 2 diabetes mellitus (DM2), overweight, obesity, metabolic syndrome, among others. In presence of a more competitive female population with wider access to the labor market, social, economical, and psychosocial factors have been added to increase CV risk in women.

ETHYOLOGY AND PATHOGENESIS OF DYSLIPIDEMIA IN WOMEN

Lipidic profile during a woman's lifetime

During their lifetime, women experience hormonal changes, from puberty, reproductive age, and perimenopause to menopause stages. These changes induced variations in the amounts of blood lipids. After birth, LDL concentrations are about 65 mg/dL, in both men and women, progressively increasing in the first two years. Men and women have similar levels of cholesterol in this age, but in teenagers, ranging from 10 to 17 years old, the LDL concentrations are lower in men than in women. After 20 years of age, both men and women show an increase in their LDL concentrations, greater in men than in women. Interestingly, when men and women achieve

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mature adulthood, the HLD-c level is lower in men compared to women, resulting in a cardioprotective factor for women at this age.

It is relevant to consider the modifications that the lipid profile show during pregnancy, in which an increase of the hormones gonadotropin, β-estradiol, insulin, and progesterone occurs. These hormones are associated with an increment of total cholesterol (TC), TG, LDL-c, HDL-c, and apoprotein A1 concentrations, having their highest peak at the week 36 of pregnancy.

In studies made in women with high-risk pregnancies, dyslipidemia was related to a 3.6 times higher risk of preeclampsia development (PE). Also, PE has a strict relationship with pre-pregnancy dyslipidemia. HTG has also been related to a 1.6 probability increase of PE. Although to date there is no direct mechanism explaining the role of dyslipidemia and PE, probably endothelial dysfunction is the cause. In a study carried out in the IMSS (Mexican Institute of Social Security), were studied two groups (each of 100 patients) of pregnant women. Divided in those with normal pregnancy and the other with PE. The essay found that in PE, there were more patients with severe rise of TG and very low density lipoproteins (VLDL). In another study, the relevance of the lipidic profile during the third trimester of high-risk pregnancy in women between 18-50 years old and their children was determined. About 83.9% of women presented alterations in lipid metabolism. The study concluded that dyslipidemia in pregnancy is related with comorbidities such as DM2, hypertension, smoking, obesity, and preeclampsia. Among other pathologies that should draw our attention is the polycystic ovary syndrome (PCOS), an endocrinological disorder found at a reproductive age, associated with obesity, fertility problems, hyperandrogenism/hyperandrogenemia, insulin resistance and dyslipidemia. The most relevant changes in the lipid metabolism in women with PCOS are increase of the LDL-c, the decrease of the HD-c, and the increase of the TG concentrations.

Other stages that nowadays have become a challenge for cardiology are pre-menopause and menopause, where the expression of risk factors joined the hormonal suppression, facts that forces cardiologists to have a multidisciplinary vision of the practice. The evaluation of the lipidic profile in menopause women is modified due to changes produced by aging and hypoestrogenism, resulting in a proatherogenic state, that expresses with the following traits: Increment of LDL-c and TG, with decrease of HDL-c. The intermediate density lipoproteins (ILD) concentrations are also related with the rise of CV disease in menopause women.

RELATIONSHIP BETWEEN THE LIPID METABOLISM AND ESTROGENS

The production of estrogens it is mainly performed by ovaries. In the bloodstream, estrogens have low affinity binding with albumin. They require for their mobility the action of sexual hormone transporting globulin (SHBG) and the corticosteroid transporting globulin (CBG). Estrogen actions define the main gender sexual characteristics, the psycho-emotional state, the bone metabolism, inhibiting the action of the osteoblasts, fat biosynthesis and proteins. Regarding lipid metabolism, they increase HDL-c, diminishing TG, and LDL-c. Also, the pancreatic β-cells sensitivity is augmented, with a decrease of insulin resistance. Among other actions, estrogens produce an increase of the blood flow at a cerebral level, inhibiting amyloid deposits formation.

Estrogenic action. The estrogens act through at least 2 independent steroid receptors placed in the cell nucleus or in the membrane. In turn there are two nuclear types, the estrogen receptors (ER) α and β, structurally different, and their location vary in the tissues. The steroid activation depends on the plasmatic concentrations of the free hormone, as well as, the receptor affinity. The ER-α plays a key role in the cardiovascular system, the liver, the hypothalamus, endometrium, cerebral cortex, adrenal gland, endothelium, and smooth vascular muscle. It is a prominent agent for CV protection. On the other hand, ER-β causes vasodilatation, neovascularization. and inhibition of cellular apoptosis in cardiac muscle.

ER-α has many polymorphic variables. There are two significant polymorphisms of the alpha receptor (XBA-1 and PVull). The

latter polymorphism is related to alterations in bone mineralization (osteoporosis), CV system, endometriosis, breast cancer, changes in the lipid profile, hypertension, and coronary atherosclerosis.

The Rotterdam study involving 4,000 women found that those with the genotype IVS1-397TT, faced a high risk for developing heart disease, while those with the genotype PVull TT were prone to weight increase, hypertension and DM2.

LIPID PROFILE INDICATORS IN WOMAN AND HEART DISEASE RISK

The study of women with dyslipidemia must be integral. Clinical evaluation let identify the traditional risk factors for both men and women like, age, hypertension, smoking, dyslipidemia, DM2, physical conditions, sedentary behavior, diet, and family history of disease, among others. Clinical study, ss well, unveil non-traditional factor gender-related, such as risky pregnancies, autoimmune disorders, chronic kidney disease, chest wall radiation, cardiotoxic chemotherapy, and the like. Hormonal factors as premature menopause, menopause, hormone therapy, polycystic ovarian syndrome, obesity, and cardio-metabolic risk also are revealed in the basic clinical examination. Added to these factors, the social determinants of health that intervene in an important way are, ethnicity, education, income, living conditions, etc., and on the other hand, psychological risk factors such as, depression, anxiety, loneliness, perceived stress, that through diverse mechanisms increase cardiovascular risk. Finally, it should be mentioned the main responsible factor of chronic inflammation, endothelial dysfunction, and the existence of subclinical atherosclerotic lesions. Both silent processes are behind are behind the threat of the clinical expression of atherosclerotic CV diseases (ASCVD). It is important to mention that early stage identification of CV risks starts in routine check-ups, complemented by laboratory studies, as identification of biochemical risk markers, such as glycemia, glycated hemoglobin, kidney damage, and lipid profile.

In patients with chronic kidney disease, the most frequent lipid alterations are the increase of TG and low of HDL-c, raising of LDL-c and TC are less significative.

Women with autoimmune diseases like; rheumatoid arthritis, erythematous lupus, anti-phospholipid syndrome, distinguish themselves for showing, at an earlier age, and with high frequency, ASCVD, and cardiovascular mortality in higher rates.

In women with DM2, the usual lipid profile found is HTG, low HDL-c and the arise of LDL-c with mor proportion of smaller, denser and more atherogenic particles. Hypothyroidism is commonly associated with the 56% cases of the hypercholesterolemia.

It is relevant to consider familiar hypercholesterolemia in groups of young women, since this is associated with premature coronary disease, caused by high concentrations of LDL-c. These conditions should be suspected when LDL-c concentrations are > 190 mg/dL, after excluding other secondary causes.

LIPID PROFILING IN WOMEN

The traditional lipid profile includes total TC, LDL-c), HDL-c), TG, non-HDL cholesterol (non-HDL-c); and the atherogenic indexes or quotients TC/HDL-c, non-HDL-c/HDL-C, LDL-c/HDL-c, and TG/HDL-c. It has been proposed a new ischemic indicator for women in the menopause stage, known as atherogenic index in plasma (AIP), estimated by a molar transformation of TG and HDL-c concentrations ratio. The index is an independent predictor for cardiovascular disease risk in women post-menopause, related to the size lipid particles.

In the recent past, imaging techniques become useful for the patient's CV risk re-stratification. Detection of coronary artery calcification by non-contrasted computed tomography (CT scan), femoral or carotid ultrasound, and many others imaging studies are excellent supporting clinical tools, whose description is beyond the limit of this text.

DISLIPIDEMY TREATMENT IN WOMEN

The treatment for patients with dyslipidemia should not only be integral and multidisciplinary, but must include lifestyle changes, mainly

eating habits. For all patients it is advisable the following recommendations:

1. Fatty acids ingest reduction to less than 10% of the total energetic intake, and preferably replacing them with polyunsaturated fats. Avoid highly processed foods. Fats must represent less than 30% of the total calorie intake. Reduction the consumption of simple and complex carbohydrates, specially the refined ones, and also avoid the excessive consumption of alcohol.
2. Reduce the amount of salt intake (average 5 grams of salt per day).
3. Consumption of fiber.
4. Increase physical activity, as it has multiple health benefits such an increase HDL-c concentrations, decrease of TG concentration, maintaining healthy weight contributes to enhances CV health.
5. Quit smoking as a priority. Mainly in women with low HDL-c.

Pharmacological treatment

The main criteria exposed in the Dyslipidemia Study Guidelines by the European Society of Cardiology (ESC) on 2019, as well as the US American guidelines ACC/AHA, do not specify the treatment considering the patient's gender. Women have less possibilities of receiving treatment with statins than man, as well as, more of them abandon the treatment or receive insufficient dosing.

Studies with statins in primary prevention in women have been controversial. The recommendations in primary prevention of CV disease in women are shown in *Figure 1*.
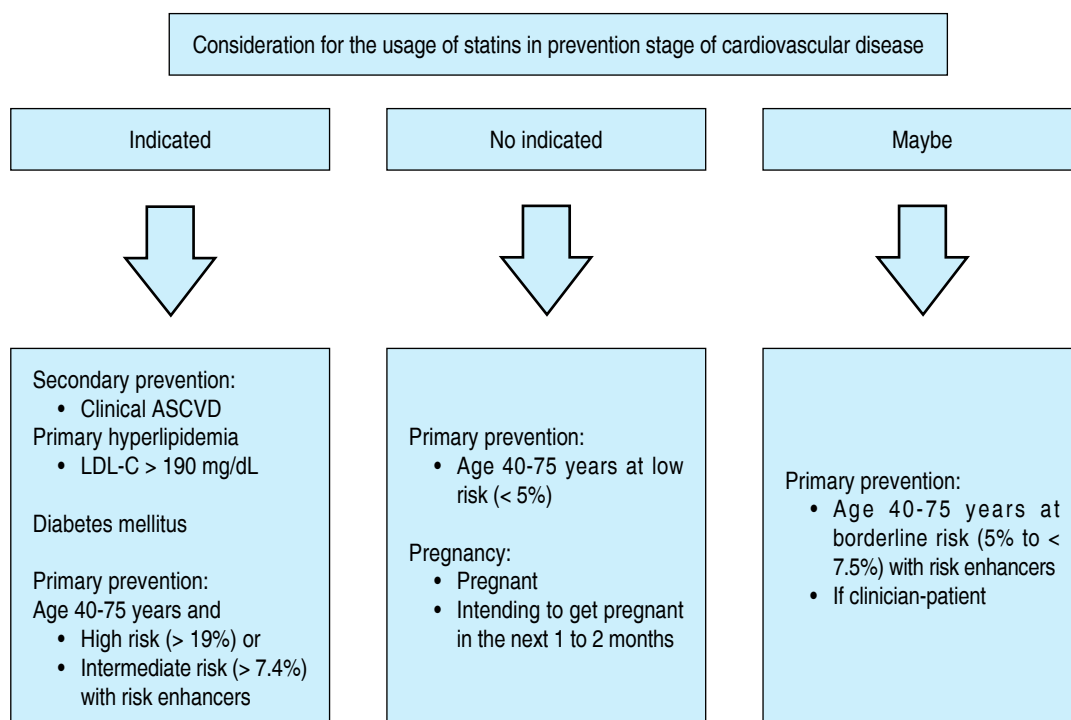
The STELLAR study confirms the statin treatment efficacy, diminishing the LDL-c in a range of 21 to 57%, in a six-week period, depending on the statin and dosage used. The study concluded that statin therapy is efficient to reduce CV events in women, like what happens in men. Both STELLAR and JUPITER Study support the usage of rosuvastatin in primary prevention. The latter study showed the beneficial effects of rosuvastatin in subjects with elevated concentrations of high sensitivity c-reactive protein individuals of both genders.

The therapy combined with ezetimibe (inhibitor of intestinal absorption of cholesterol and phytosterols) and high or medium effect statin have been prescribed mainly in patients

Figure 1:

Considerations about the use of statins for cardiovascular disease prevention.

Modified from: Cho L et al.

Consideration for the usage of statins in prevention stage of cardiovascular disease

Indicated	No indicated	Maybe

Secondary prevention:
• Clinical ASCVD
Primary hyperlipidemia
• LDL-C > 190 mg/dL

Diabetes mellitus

Primary prevention:
Age 40-75 years and
• High risk (> 19%) or
• Intermediate risk (> 7.4%) with risk enhancers

Primary prevention:
• Age 40-75 years at low risk (< 5%)

Pregnancy:
• Pregnant
• Intending to get pregnant in the next 1 to 2 months

Primary prevention:
• Age 40-75 years at borderline risk (5% to < 7.5%) with risk enhancers
• If clinician-patient

that require a quicker effect control, also to diminish the secondary effects.

PCSK9 inhibitors, in the treatment of dyslipidemia in women. Several studies (FOURIER, ODYSSEY OUTCOMES, SPIRE) have not shown any gender differentiated response to these innovating drugs. These inhibitors will be described in detail in other section of this text. The management of HTG in women, depends on the associated factors, as well as the type of lipid disorder. It is important to mention that in pregnancy, mainly in the last trimester they could rise, for which diet measure should be reinforced. The usage of fibrates (gemfibrozil) is limited to people with high triglyceride risk > 500 mg/dL. limited to people with high level triglyceride (>500 mg/dL) with high risk of pancreatitis. Nowadays, multiple multicentric studies are focused on the use of omega-3 fatty acids, like eicosanpentanoic (EPA) and docosahexaenoic (DHA).

CONCLUSIONS

Dyslipidemia is very common in feminine adult population, phenomenon magnified in the menopause stage. In this moment, dyslipidemia in consonance with other risk factors, skyrocket, in exponential fashion, the ASCVD risk. In most of the large studies on lipids and ASCVD, women are underrepresented. The dyslipidemia treatment in primary and secondary stages, is plagued of shortcomings: absence or delay of lipid-lowering drugs prescriptions, inadequate doses, and more frequent abandon of treatment. Finally, the combined therapies should be a reasonable option to attain therapeutic goals. Also, physicians should not ignore the advice on therapeutic modifications of lifestyle. This point should be always a priority in medical practice.

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