Editorial

La revista Latinoamericana de Hipertensión publica su cuarto número del volumen 2 del año 2007.

Los artículos publicados son de revisión escritos por investigadores reconocidos en el área:1) Nutrición y enfermedades cardiovasculares, por el Dr. Patricio López Jaramillo de Colombia y 2) Preeclampsia-eclampsia, por el Dr. José López Mora de Venezuela. También incluimos aportes originales sobre factores de riesgos y sobre insulina en diabetes mellitus escritos por el grupo de Maracaibo, Venezuela, liderizados por el Dr. Clímaco Cano y el Dr. Valmore Bermúdez. Todos los manuscritos fueron arbitrados.

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Alcance y Política Editorial

La Revista Latinoamericana de Hipertensión es una publicación biomédica periódica, arbitrada, de aparición trimestral, destinada a promover la productividad científica de la comunidad nacional e internacional en toda el área del Sistema Cardiovascular; la divulgación de artículos científicos y tecnológicos originales y artículos de revisión por invitación del Comité Editorial.

Está basada en la existencia de un Comité de Redacción, consistente en Editores en Jefe, Editores asociados y Comité Editorial. Los manuscritos que publica pueden ser de autores nacionales o extranjeros, residentes o no en Venezuela, en castellano o en ingles (los resumenes deben ser en ingles y castellano). Los manuscritos deben ser trabajos inéditos.

La Junta Directiva de la Revista no se hace responsable por los conceptos emitidos en los manuscritos. Los autores deben aceptar que sus manuscritos no se hayan sometidos o hayan publicados en otra revista. El manuscrito debe ir acompañado de una carta solicitud firmada por el autor principal y el resto de los autores responsables del mismo.

Forma de Preparación de los Manuscritos

Para la publicación de trabajos científicos en la Revista Latinoamericana de Hipertensión, los mismos estarán de acuerdo con los requisitos originales para su publicación en Revistas Biomédicas, según el Comité Internacional de Editores de Revistas Biomédicas (Arch. Intern. Med. 2006:126(36):1-47), www.icmje.com. Además, los editores asumen que los autores de los artículos conocen y han aplicado en sus estudios la ética de experimentación (Declaración de Helsinki). A tales efectos, los manuscritos deben seguir las instrucciones siguientes:

1. Mecanografiar original a doble espacio en idioma español, papel bond blanco, 216 x 279 mm (tamaño carta) con márgenes por lo menos de 25 mm, en una sola cara del papel. Usar doble espacio en todo el original. Su longitud no debe exceder las 10 páginas, excluyendo el espacio destinado a figuras y leyendas (4-5) y tablas (4-5).

2. Cada uno de los componentes del original deberán comenzar en página aparte, en la secuencia siguiente:
a. Página del título.
b. Resumen y palabras claves.
c. Texto.
d. Agradecimientos.
e. Referencias.
f. Tablas: cada una de las tablas en páginas apartes, completas, con título y llamadas al pie de la tabla.
g. Para la leyenda de las ilustraciones: use una hoja de papel distinta para comenzar cada sección. Enumere las páginas correlativamente empezando por el título. El número de la página deberá colocarse en el ángulo superior izquierdo de la misma.

3. La página del título deberá contener:
3.1. Título del artículo, conciso pero informativo.
a. Corto encabezamiento de página, no mayor de cuarenta caracteres (contando letras y espacios) como pie de página, en la página del título con su respectiva identificación.
b. Primer nombre de pila, segundo nombre de pila y apellido (con una llamada para identificar al pie de página el más alto grado académico que ostenta y lugar actual donde desempeña sus tareas el(los) autores.
c. El nombre del departamento (s) o instituciones a quienes se les atribuye el trabajo.
d. Nombre y dirección electrónica del autor a quien se le puede solicitar separatas o aclaratorias en relación con el manuscrito.
e. La fuente que ha permitido auspiciar con ayuda económica: equipos, medicamentos o todo el conjunto.
f. Debe colocarse la fecha en la cual fue consignado el manuscrito para la publicación.

4. La segunda página contiene un resumen en español y su versión en inglés, cada uno de los cuales tendrá un máximo de 150 palabras. En ambos textos se condensan: propósitos de la investigación, estudio, método empleado, resultados (datos específicos, significados estadísticos si fuese posible) y conclusiones. Favor hacer énfasis en los aspectos nuevos e importantes del estudio o de las observaciones. Inmediatamente después del resumen, proporcionar o identificar como tales: 3-10 palabras claves o frases cortas que ayuden a los indexadores en la construcción de índices cruzados de su artículo y que puedan publicarse con el resumen, utilice los términos del encabezamiento temático (Medical Subject Heading) del Index Medicus, cuando sea posible.

5. En cuanto al texto, generalmente debe dividirse en: introducción, materiales y métodos, resultados y discusión.

6. Agradecimientos, sólo a las personas que han hecho contribuciones reales al estudio.

7. Las referencias bibliográficas serán individualizadas por números arábicos, ordenados según su aparición en el texto. La lista de referencias bibliográficas llevarán por título "Referencias Bibliográficas" y su ordenamiento será según su orden de aparición en el texto.

Las citas de los trabajos consultados seguirán los requisitos de uniformidad para manuscritos presentados a revistas Biomédicas, versión publicada en: Ann Intern Med. 2006; 126(36): 1-47, www.icmje.com. No se aceptarán trabajos que no se ajusten a las normas.

8. Tablas: En hoja aparte cada tabla, mecanografiada a doble espacio; no presentar tablas fotográficas; enumere las tablas correlativamente y proporcione un título breve para cada una; dé a cada columna un encabezamiento corto o abreviado; coloque material explicativo en notas al pie de la tabla y no en el encabezamiento; explique en notas al pie de la tabla las abreviaturas no estandarizadas usadas en cada tabla; identifique claramente las medidas estadísticas de las variables tales como desviación estándar y error estándar de la medida; no use líneas horizontales ni verticales: citar cada tabla en orden correlativo dentro del texto; citar la fuente de información al pie de la tabla si ésta no es original.

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Todas las figuras deberán llevar un rótulo engomado en el reverso y en la parte superior de la ilustración indicando número de la figura, apellidos y nombres de los autores. No escribir en la parte posterior de la figura. Si usa fotografía de personas, trate de que ésta no sea identificable o acompañarla de autorización escrita de la misma. Las leyendas de las ilustraciones deben ser mecanografiadas a doble espacio en página aparte y usar el número que corresponde a cada ilustración. Cuando se usen símbolos y fechas, números o letras para identificar partes en las ilustraciones, identifíquelas y explíquelas claramente cada una en la leyenda. Si se trata de microfotografía, explique la escala e identifique el método de coloración.

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13. Todos los trabajos serán consultados por lo menos por dos árbitros en la especialidad respectiva.

14. La Revista Latinoamericana de Hipertensión, no se hace solidaria con las opiniones personales expresadas por los autores en sus trabajos, ni se responsabiliza por el estado en el que está redactado cada texto.

15. Todos los aspectos no previstos por el presente reglamento serán resueltos por el Comité Editorial de la Revista.

16. La revista apoya las políticas para registro de ensayos clínicos de la Organización Mundial de la Salud (OMS) y del International Committee of Medical Journall Editors (ICMJE), reconociendo la importancia de esas iniciativas pera el registro y divulgación internacional de Información sobre estudios clínicos, en acceso abierto. En consecuencia, solamente se aceptarán para publicación, a partir de 2007, los artículos de investigaciones clínicas que hayan recibido un número de identificación en uno de los Registros de Ensayo Clínicos validados por los criterios establecidos por OMS e ICMJE, cuyas direcciones están disponibles en el sitio del ICMJE. El número de Identificación se deberá registrar al final del resumen.

Are nutrition-induced epigenetic changes the link between the socio economic pathology and cardiovascular diseases?

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Abstract

The prevalence of cardiovascular diseases (CVD) and diabetes mellitus type 2 (DM 2) is decreasing in developed countries, despite the increase in the percentage of subjects with obesity and other well recognized cardiovascular risk factors. In contrast, the recent transition of the economic model experimented by developing countries, characterized by the adoption of a western lifestyle, that we have denominated socio-economic pathology, has led to an increase in the burden of CVD. It has been demonstrated that conventional cardiovascular risk factors in developed and developing countries are the same. Why then does population of developing countries have nowadays, a higher incidence of cardiovascular disease than those of developed countries, if they share the same risk factors? We have proposed the existence of a higher susceptibility to the development of systemic inflammation at low levels of abdominal obesity (AO) in population of developing countries and consequently endothelial dysfunction, insulin resistance, DM 2 and CVD. In contrast, an important percentage of obese people living in developed countries have a healthy phenotype and low risk of developing CVD and DM 2. Human epidemiological studies and experimental dietary interventions in animal models have provided considerable evidence to suggest that nutritional imbalance and metabolic disturbances early in life may later have a persistent effect on the adult's health that may even be transmitted to the next generations. Epigenetic changes dependent on nutrition could be the key in this evolutionary health behavior, acting as a buffering system permitting the adaptation to environmental conditions by silencing or increasing the expression of certain genes.

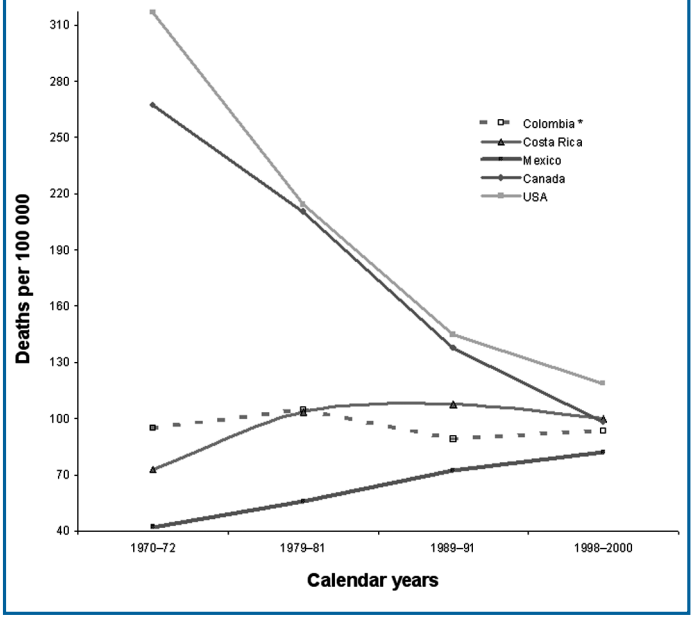
Key words: obesity, metabolic syndrome, epigenetic, adaptive response, socio economic pathology.

Introduction

Worldwide, cardiovascular diseases (CVD) are the leading cause of death. It is calculated that 3.8 million men and 3.4 million women die each year of this cause [1]. Moreover, an increase from 47 million disability-adjusted life years in 1990 to 82 million, is globally projected for 2020 [2]. Although age-adjusted cardiovascular death rates have declined in several developed countries, rates of CVD have greatly risen in low and middle-income countries, with about 80% of the burden now occurring in the latter [3]. It has been estimated that 5.3 million deaths attributable to CVD occurred in developed countries in 1990, against 8 to 9 million in developing countries[4]. In USA, between 1972 and 2002, the CVD death rate declined by 54%, specially due to the decline in coronary heart disease (CHD) and stroke mortality (62%[5]).

In contrast, in Colombia, the death rate for CHD in 20-84 year old subjects increased from 58.5 per 100.000 in 1980 to 103.2 in 1996. Only 30% of this increase could be attributed to population aging[6]. From 1997 to 2001 acute myocardial infarction (AMI), stroke and diabetes mellitus type 2 (DM 2) were responsible for 213.150 deaths (19.6%). Together, these deaths exceeded those due to violent causes, which for several years were the first cause of death in this country (Figure 1).

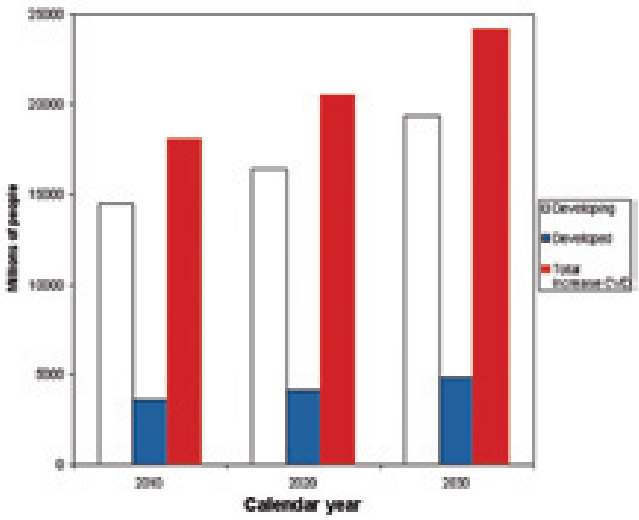
Figure 1. Trends in death certification rates per 100.000 inhabitants for coronary heart diseases in 5 countries of the Americas in different stages of development 1970–2000



Adapted from Rodriguez T, Malvezzi M, Chatenoud L, Bosetti C, Levi F, Negri E, La Vecchia C. Trends in mortality from coronary heart and cerebrovascular diseases in the Americas: 1970-2000; Heart. 2006 Apr;92(4):453-60

In the last years the transition in life style experimented by developing countries due to the adoption of a western economic model, with an increased exposure to risk factors such as high saturated fat diets, sedentarism, psycho-social stress and cigarette smoking has led to an increased prevalence of obesity, alteration in lipid profile, in plasma glucose and high blood pressure[7] which could explain in part the CVD epidemic observed in those countries (Figure 2). We have proposed that the recent exposure to these changes determines a higher degree of biological bad adaptation which entails a greater risk of CVD. The shorter the exposition to the new lifestyles, the less the biological adaptation and the higher the risk of CVD. We have proposed to call this process socio-economic pathology, to express the interaction of socio-economic factors and classic cardiovascular risk factors with the length of time of exposition of a particular society to the western lifestyle[8].

Figure 2. Projected annual trends in CVD deaths in populations at different stages of development 2010–2030



Adapted from Mackay, J; Mensha, G, A; World hearth organization (WHO), Center for Disease control (CDC)¨ The atlas of heart disease and stroke¨ the future and the past;(CDC).

Cardiovascular risk factors in developing countries

A large study realized in Brazil identified that conventional cardiovascular risk factors such as hypercholesterolemia, smoking, hyperglicemia and obesity are associated with AMI in this population[9]. The INTERHEART study[10] identified the risk factors associated with AMI in 52 developed and developing countries. Smoking, hypertension, abnormal lipids, abdominal obesity (AO), diabetes and psychosocial stress were associated with ischemic disease in all regions of the world with no differences in age and gender. However, Lanas et al.[11] reported the results from 1237 Latin American subjects from Brazil, Argentina, Chile and Colombia, included the INTERHEART study, demonstrating that central obesity was the most important risk factor associated with AMI in this population, much more than in the entire population of the study. We believe that the biological response to obesity in developed countries is different than in developing countries, and that this response is modulated through epigenetic regulation.

Is Population from developing countries more susceptible to the inflammatory effect of abdominal obesity?

The relationship between obesity and incidence of CVD was established several years ago. The Framingham cohort demonstrated that obesity is an independent predictor of CVD in both sexes[12]. This relation became more evident in subsequent studies[13]. The IDEA study, realized in 63 countries with 170.000 subjects in primary care, concluded that for an increase of 14 cm in waist circumference for men and of 14.9 cm for women, the probability of CVD rose by 21% to 40%[14]. Two cohort studies performed in Korea[15] and United States[16], established

that not only is obesity but also overweight the main risk factors associated with the risk of death, in subjects that have never smoked.

The National Cholesterol Education Program Adult Treatment Panel III (NCEPT-ATP III) recognized overweight and obesity as major underlying risk factors for CVD, AO being more highly correlated with CVD than body mass index[17].

The International Diabetes Federation (IDF) established the presence of AO as an obligatory criterion for the diagnosis of metabolic syndrome (MS), which is strongly related with the development of DM 2 and CVD. Moreover, the IDF has proposed a different threshold for waist circumference depending on regions and ethnic groups[18]. In the Andean population with no previous CVD history, our group reported that criteria for MS proposed by IDF is more useful to identify subjects with MS than ATP-III criteria[19].

In addition, several studies carried out in developing countries have reported lower waist circumference cut-off points associated with cardiovascular risk than those reported in developed countries. Misra et al [20], reported higher risks of cardiovascular events among Asian Indians with waist circumference of ≥90 cm and ≥80 cm for men and women, respectively. Similar results have been obtained in Latin American countries[21; 22]. In healthy young Colombian men a waist circumference of 88 cm identified subjects in cardiovascular risk with a sensitivity of 83.7% and a specificity of 84.8%[23]. In Ecuador, it was demonstrated that a waist circumference of 90 cm in men is the best cut-off point associated with the presence of at least two other MS criteria according to the NCEPT-ATP III[24].

The study Abdominal Obesity as a Risk Factor for Coronary Artery Disease, (ABOCAD) performed in Colombia, demonstrated that a waist circumference of 94 cm for men and 84 cm for women is an independent risk factor associated with coronary artery disease, defined as at least a 50% reduction of the internal diameter of the secondary coronary arteries or a 30% reduction of the main coronary arteries.

Waist circumference has demonstrated to be an easier parameter to evaluate the content of visceral fat, which is the main source of pro inflammatory cytokines[25,27]. These adipokines are elevated in serum of obese subjects [28] and it has been proposed that the systemic inflammation produced by the adipose tissue participates in all stages of the development of atherosclerosis such as endothelial dysfunction[29], atheroma formation, rupture of plaque and acute thrombotic complications[30]. C-reactive protein (CRP), produced by the liver in respond to the stimulus of tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6) are increased in subjects with multiple acute coronary events and are a strong independent predictor of new acute coronary events[31]. We have demonstrated in the Andean region that CRP is an independent risk factor for essential hypertension[32] and pregnancy induced hypertension[33,34]. Moreover, the concentration of CRP, IL-6 and TNFα are increased in dislipidemic subjects with MS [8; 35] and in overweight and obese children[36]. Regardless of the differences in the methods to quantify these inflammatory markers we have observed that in general the concentration of the proinflammatory cytokines is higher in our population than that reported in the population of developed countries [8]. For this reason we have proposed that the systemic inflammation associated with AO is increased in population of developing countries at lower levels of AO. Further cohort studies in developing countries with the enrollment of a large population are necessary to confirm this proposal, and whether the population of these countries has a major risk of developing atherosclerosis and CVD with lower levels of AO[37].

The obese metabolically healthy: An observation of developed countries

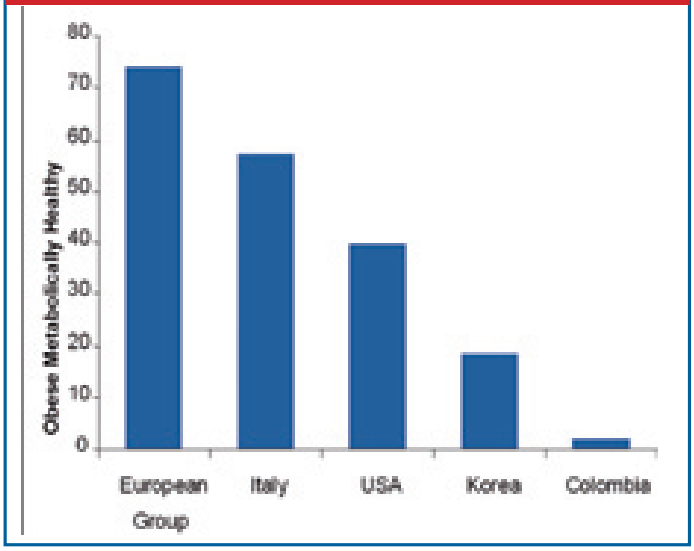
Abdominal obesity has been found to have a major correlation with a cluster of diabetogenic, atherogenic, prothrombotic and metabolic abnormalities[38]. Obesity is strongly associated with other chronic metabolic diseases and insulin resistance[39]. However, a subset of obese subjects that have a low risk of developing CVD has recently been reported. These subjects, termed obese metabolically healthy (OMH) despite the increase in fat tissue, have a healthy metabolic profile, including normal insulin sensitivity[40]. Several large studies performed in developed countries have demonstrated a high prevalence of obese subjects without insulin resistance (IR)[41,43]. Ferranini et al[41] enrolled 1146 Caucasian men and women whose insulin resistance (or sensitivity) was measured by the euglycemic insulin clamp technique. Only 26% of all obese individuals with any metabolic disorder were IR. Another large study[42] performed in Italy evaluated insulin sensitivity using the homeostasis model assessment (HOMA), demonstrating that 57% of the obese subjects were healthy and showed no IR. McLaughlin et al. reported that 30% of 465 apparently healthy individuals had normal insulin sensitivity, though either overweight or obese[43].

Subsequently small studies[44-46] performed in USA, Canada and Korea have reported a 20 to 40% prevalence of OMH women. The healthy metabolic profile in these obese women is characterized by normal blood pressure, high level of high density lipoprotein (HDL)-cholesterol, low levels of fasting triglycerides, normal fasting insulin and fasting glucose, as well as normal insulin sensitivity[44,45]. In addition, it was demonstrated that these healthy and obese women

had significantly less visceral fat (as measured by computed tomography) and lower levels of CRP, IL-6 and oxidized LDL than women metabolically abnormal[45;46]. These differences were not significant anymore after CRP levels were adjusted for the content of visceral fat[46]. We can speculate that OMH showed a healthy profile due to a special phenotype that expresses less or smaller visceral adipocytes, which are less proinflammatory and metabolically active. In support of this proposal, some studies have demonstrated that the growth of adipocytes is associated with substantial changes in metabolic functions such as cholesterol metabolism[47] and response to insulin[48]. In addition it has been demonstrated that hypertrophic adipocytes produce an important systemic inflammation[49], increasing the risk of metabolic and cardiovascular complications[50;51]. Thus, the lower proinflammatory activity of the adipocytes in OMH individuals might confer a lower risk of CVD. Recently, in a study done in Canada[52] with a cohort of 1824 non diabetic men, free of ischemic heart disease (IHD) that were followed for a period of 13 years, obesity per se didn't increase the risk of IHD, but did so when IR was present. This result suggests that IR is a key element to increase the risk of CVD in obese subjects. In the absence of IR obese subjects don`t have an increased risk of CVD.

The studies currently published on OMH subjects have been carried out in developed countries. In Colombia, in a sample of 579 abdominal obese subjects according to IDF criteria, we identified only 1.7% of individuals with AO and without IR. The other 98.3% of subjects met all the criteria for MS. This result supports the proposal that the population of developing countries, due to biological adjustment for the recent changes in its life style imposed by the economic western model, has become prone to develop IR, and the visceral fat prone to produce a systemic inflammatory response. On the other hand, populations of developed countries with a longer exposure to western life style have developed mechanisms of adaptation associated with the presence of visceral adipocytes that secrete anti-inflammatory citokynes, such as adiponectine, a substance which maintains an adequate sensibility to insulin, thus contributing to a smaller number of obese subjects with IR and a higher number of OMH subjects (Figure 3). Large prospective studies will be necessary to confirm this hypothesis although some already published data from developed countries support this proposal. Brochu et al[44] evaluated the presence of IR in obese postmenopausal women. The authors employed a multiple regression analysis to identify independent factors that distinguished OMH subjects from those with abnormal metabolic profile. The major independent factor was low amounts of visceral adipose tissue. Interestingly, 13% of the variation observed in the normal insulin sensitivity was an earlier age-related onset of obesity (between 13-19 years of age). This finding is in line with the results reported by Muscelli et al.[53] who observed that in obese subjects with preserved glucose tolerance, the relationship between the duration of obesity and the insulin sensitivity was directly proportional, irrespective of the degree of obesity. Moreover, in a longitudinal study realized in a developed country,it was demonstrated that gain weight during childhood was associated, contrary to expected, with reduced risk of CHD in adulthood[54]. Globally, these results suggest that human beings develop an adaptive response to new environmental and nutritional conditions and that this response is dependent of the time that a determinate society has been exposed to the new conditions.

Figure 3. Prevalence of obese subjects metabolically healthy



Adapted from: Ferrannini et al. J Clin Invest 1997; 100:1166-1173. Bonora et al. Diabetes 1998; 47:1643-1649. Brochu et al. J Clin Endocrinol Metab 2001; 86:1020-1025. Shin et al. Int J Obes (Lond) 2006; 30:1529-1534.

What are the mechanisms of the adaptive process?

Most living organisms acquire tolerance when they are exposed to subletal environmental alterations[55]. When this behavior is used to protect the tissues it is named preconditioning (PC). This response is observed in a vast variety of species from bacteria to mammalian cells. For example, the ischemic preconditioning, protects the brain cells from ischemic damage provoked by prolonged ischemia[56]. In the heart, transient ischemia induces myocardial protection against subsequent ischemia and reperfusion injury[57].

It has been proposed that the heart possesses an ability to adapt to stress by changing its phenotype, making it more resistant. There are evidences of adaptation of the heart to brief coronary stress (ischemic, exercise, heat stress, rapid ventricular pacing and other types of stress). Moreover, it was found that PC is a biphasic phenomenon that protects in the early stage of the stress against myocardial infarction and in the later phase, against myocardial infarction and myocardial stunning[58].

In fact, PC is the result of a cascade of cellular events, that activates an ¨alarm system¨ against an imminent injury, and induces a defensive phenotype that represents a complex response requiring synchronized activation of several genes[58].

It is interesting to speculate that the phenomenon of PC could explain the inverse relationship between the number of obese people and CVD in developed countries: the prevalence of obesity increases but the cardiovascular mortality decreases[1-7; 59]. In addition, it has been proposed that one of the reasons for the increase in life expectancy is that our genome permits adaptation to different conditions and environments[60]. Although genetic factors might predispose to CVD, not all people genetically predisposed develop it, which suggests that there are environmental factors that regulate this relationship[61-65]. Moreover, the World Heart Organization reported that 80% to 90% of people dying from coronary heart disease have one or more major risk factors influenced by their lifestyle[1].

Nutrition induced epigenetic changes: the situation in developed countries

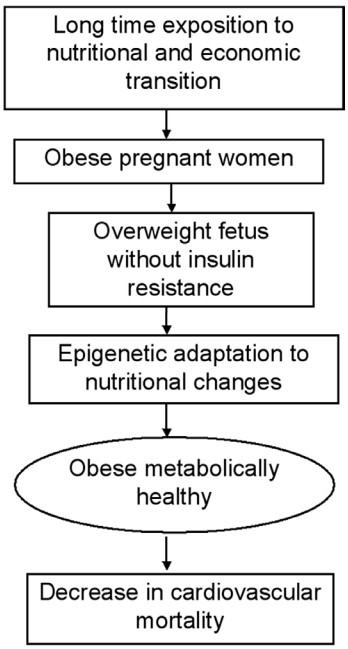
Populations all over the world are permanently exposed to changes in food intake from conception to death. Several decades ago it was proposed that a genetic component could be responsible for differences in dietary response[61]. Recently the interaction between nutrition and gene expression has been examined[61-63]. Dietary habits represent a key environmental factor that modulates gene expression throughout life[64]. Therefore, a better understanding of the interaction of genetic and environment in the association between CVD and insulin resistance could help to prevent MS and CVD[65;66]. Epigenetic is the science that explains the variation of genes expression in response to changes in environmental conditions[64]. This term includes any process that alters gene activity without changing the DNA sequences, and leads to rapid modifications that can be transmitted to daughter cells, although, some epigenetic changes can be reversed[65]. Epigenetic modulation of gene expression serves as a defence mechanism against harmful agents, so that genes can be silenced or expressed by various types of epigenetic processes such as methylation and acetylation[66]. DNA methylation is the process whereby an area of a chromosome known to be a regulatory region for a specific gene is methylated, process that inhibits the gene expression and consequently isn't transcribed into messenger RNA. Another epigenetic process is chromatin modification. Chromatin is the nuclear complex consisting of DNA wrapped around histone proteins which can be modified by substances such as acetyl groups (acetylation) and enzymes to influence gene expression[67].

Cooney et al.[68] reported that a diet supplemented with methyl donors in pregnant mice influences epigenetic variation and DNA methylation of offspring, affecting their health and longevity. This result argues that an environmental stimulus early in life can change the stable expression of genes and affect the phenotype of the adult.

Actually, it is not yet clear what is the participation of epigenetic in the physiopathological mechanisms of IR and MS. However, there is available information about how maternal diet or other in uterus/postnatal exposure may "program" susceptibility to later development of CVD in adulthood. There is no doubt that the exposition to harmful agents during pregnancy makes that living beings adopt several strategies to optimize their chances of survival, using genetic plasticity[69;70]. When the environment change becomes a permanent and transgenerational condition, living beings must create new strategies to guarantee their survival. We believe that it is the case of the OMH. There is not much available information about the theory that populations that are exposed for several generations to fat rich diet or to junk nutrition and obesity, acquire with time adaptive mechanisms that provide cardiovascular protection. In a study where pregnant sows were fed a standard gestational diet or an atherogenic gestational diet and their offspring maintained on either a standard diet or an atherogenic diet until the pubertal age (5 months), all offspring that received atherogenic diet had greater serum cholesterol concentration and aortic fat deposition compared with those on the standard diet. However, piglets from sows fed a standard diet that in postnatal life were fed an atherogenic diet, were the only ones that developed early coronary atherosclerosis, whereas those prenatally exposed to the fat diet and maintained on the same diet had no evidence of aortic lesions despite being hypercholesterolemic[71]. In another study, rats were fed a fat rich diet or normal chow throughout pregnancy and lactation. The vascular function was assessed at 180 days of age in mesentery arteries using endothelium-dependent dilation to acetylcholine. The offspring of fat fed dams raised on the same diet conserved the endothelial function and had lower heart rate in comparison with offspring of standard diet dams raised on the same diet or with offspring of fat fed dams raised on standard diet. However, the early and continue exposition to a fat diet in one generation does not prevent the increase of blood pressure[72]. Gallou-Kabani, et al.[73] evaluated in rats, the transgenerational effect of obesity and nutrition. The second generation of female rats, from obese mothers that were exposed to a high fat-diet at 1 month of age, developed a resistance to a high fat-diet at 6 months of age, characterized by complete protection against hyperglycemia, obesity and hyperinsulinemia but incomplete protection

against hypercholesterolemia. These experimental works are reflecting some of the data observed in the human OMH. More studies are necessaries to fully understand the process involved in the epigenetic adaptation induced by nutrition that results in an OMH (Figure 4).

Figure 4. The effect of enviromental factors in the development of cardiovascular diseases and related conditions in developed countries



Nutrition induced epigenetic changes: the situation in developing countries

In rodents, maternal dietary restriction (i.e. low protein diet) or high fat over-feeding during pregnancy or/and suckling period, gives rise to an offspring phenotype predisposed to the development of adulthood CVD[74]. This phenotype may include some components of MS such as: high blood pressure, abnormal serum lipid profiles, increased adiposity, hyperinsulinemia, abnormal glucose homeostasis, endothelial dysfunction and atherosclerosis[75,82]. Moreover, maternal diet manipulation in rats produces disturbances in the development of the endocrine pancreas[83,87]. Poor development of the pancreas and IR as a response to intrauterine malnutrition may be useful for survival in early life; however it may become a risk factor for glucose intolerance and diabetes in adulthood[88-90].

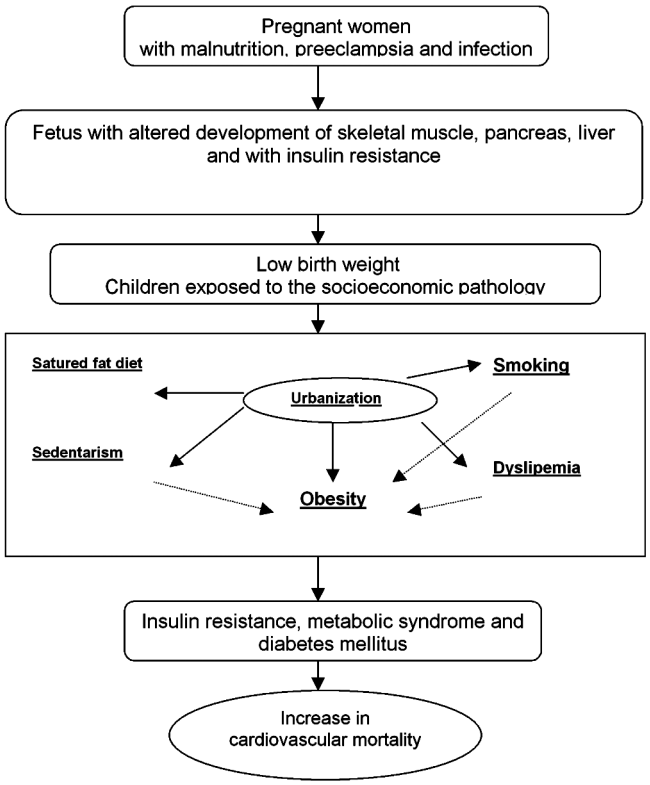
B-cells mass is decreased in rats´ offspring exposed to a low protein diet associated with an increase of apoptotic rate and a reduction of islet cell proliferation, along with an alteration in the development of islet blood vessel[83,88]. Impaired pancreatic β-cells development may cause a lasting reduction in the insulin-secretor response. However the exhaustion of the low β-cell mass may only be clearly revealed when the insulin produced by the pancreatic β-cells is not enough to maintain a normal glucose homoeostasis. Aging, obesity or pregnancy augments insulin demand, increasing the risk of hyperinsulinism, IR and DM 2[88,90].

Epidemiological studies and clinical observations have permitted to understand the relationship between under nutrition during fetal life and chronic diseases in later life. Low birth weight has been linked to adulthood heart disease, hypertension, DM 2, IR, vascular dysfunction, obesity and dyslipidemia[91,96]. A possible explanation of this phenomenon may be the thrifty phenotype hypothesis, proposed by Neel in 1962 in base of observations realized in developed countries after the second ward world[97]. This hypothesis proposed that, in response to a poor nutrition in intra uterus life, a predictive adaptive response is made by the fetus to maximize uptake and conservation of any nutrients available, resulting in a conservative metabolism with impaired growth of cells and organs. When the infant is exposed to a similarly deficient postnatal diet to that experienced in uterus, the programming of the thrifty phenotype confers a ´predictive adaptive´ advantage, since these individuals are then biologically prepared to withstand poor diet. The problem arises when postnatal diet is adequate or plentiful and exceeds the range of the predictive adaptive response[67,98].

Experimental models have shown that a poor fetal growth, followed by postnatal catch-up growth is associated with reduced average longevity in mice[99]. In humans, a longitudinal analysis performed in 3641 boys demonstrated, that the subjects with a low weight at birth who achieved an average or above average body mass at the age of 7 years on, had higher death rates from coronary heart disease[100]. Rapid weight gain in infants that were small and low weight at birth may lead to an unfavorable body composition with disproportionately high fat mass in relation to lean body mass, which could in turn lead to insulin resistance[101].

These studies support our proposal of the socio economic pathology as the cause of the epidemic of obesity, MS, DM2 and CVD in developing countries. Thus, this epidemic is associated with a recent socio economic and nutritional transition in a period of time not long enough to provoke an adaptive response and epigenetic changes to the excess of fat in the diet (Figure 5).

Figura 5. The effect of environmental factors in the development of cardiovascular diseases and related conditions in developing countries



Conclusions and hypotheses

Developing countries are nowadays going through the economic process and the changes in life style experimented few generations ago by developed countries. After several generations exposed to the harmful environment the population of developed countries has achieved epigenetic adaptation. This might be the explanation to the phenomenon of the OMH observed in an important percentage of obese individuals of developed countries. Comparative studies including population of developed and developing countries are necessary to understand better the different epidemiological behaviors observed in the CVD profile of populations with different lengths of time of exposition to new life styles.

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Increased levels of Lp(a) are related with family risk factors of CVD in children and adolescents from Maracaibo (Venezuela)

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Abstract

Objective: The aim of the study was to determine Lipoprotein (a) (Lp(a)) concentrations in a sample of subjects from Maracaibo (Venezuela) and to find out the relationship of family risk factors for cardiovascular disease and their Lipoprotein(a) levels.

Methods: 227 healthy individuals between 5 and 19 years f age, of both genders and multi-ethnic origins were selected. A complete background clinical chart and laboratory test was made for each patient in order to discard cardiovascular diseases and confirm their healthy state. The Lp (a) concentration was determined using the double antibody ELISA method. For inferential statistical analysis one factor ANOVA tests and "t" student test for independent observations were used according to each case, considered significant when p value was <0.05.

Results: No significant differences were observed when evaluating Lipoprotein (a) levels according to sex in all ages. Males showed no significant difference in Lipoprotein (a) levels between groups but, in females a significant lower level ($p<0.03$) in the group of 5-9 years was found. When considering only age, significant lower levels were observed ($p<0.03$) in the 5-9 years old group. When studying family risk factors of cardiovascular diseases, it was found that group with family risk factors had a significantly higher Lipoprotein(a) concentration ($p<0.01$) than those without family's risk factors, observing that those who had 4 or more factors exhibited a significant higher concentration, than those with 2-3 risk factors (30.6±4.5 mg/dl vs 18.5±12.2 mg/dl, $p<0.009$) and than those with 1 risk factor (30.6±4.5 mg/dl vs 21.6±1.4 mg/dl, $p<0,03$)

Conclusion: These results emphasize the clusters of family's risk factors of cardiovascular disease with higher Lp(a) levels and also indicate that the evaluation of its concentration should be taken as an independent risk factor of atherosclerosis for the population in developmental ages.

Key words: risk factors, children, Lpa, adolescents.

Introduction

Even though cardiovascular disease (CVD) does not manifest itself until adulthood, CVD risk factors, such as abnormalities in plasma lipoprotein levels, obesity and elevated blood pressure, could be present in childhood[1] and persist into adulthood[2]. Moreover, CVD risk factors are related with the presence of atherosclerosis in children and young adults[3,5]. Among CVD risk factors, elevated levels of Lp(a) constitute a well established independent risk factor - even in the presence of normal cholesterol and triacylglyceride concentrations - for Coronary Heart Disease (CHD)[6,9], influenced by proatherogenic and prothrombotic factors, both genetic and environmental, including age, sex, race, and ethnic background[10].

Lipoprotein (A) [Lp(a)] is a lipid particle that's made of phospholipids, cholesterol, and apolipoprotein B-100, with apolipoprotein(a) attached to the latter by a disulfide bond[11,12]. Similar to LDL, Lp(a) when oxidized may promote atherosclerosis by initiating the formation of foam cells which release growth factors. Lp(a) acquires a pathogenic profile on entering the arterial cell wall as a result of the influence of factors operating in the inflammatory environment of the atheromatous vessel, such as proteolytic enzymes of the metalloproteinase family[10,13].

An example of the effect of sex is provided by Ariyo et al in a prospective study in which plasma Lp(a) level was an independent predictor of cardiovascular events and death from all causes in men but not in women; however, no explanation for the observed difference was given[14]. Also Bovet et al in their study of black and white populations found an association of higher age and female gender with higher Lp(a) levels in adults[15]. The Bogalusa Heart Study found a

small but significant gender difference and a weak positive correlation with age in white girls 11-17 years of age[16]. Strong J. reported a progression of Lp(a) concentrations with age, which probably reflects a maturation phenomenon that may be influenced by gender[4]. Conversely, neither consistent associations by age or gender with Lp(a) concentration were found in NHANES-III below age 20 nor at the data showed from De Simone et al in a cohort study of children aged between 4 and 15 years according to sex, age and body composition[12,17]. Lp(a) plasma or serum levels above 30 mg/dL were associated with increased risk of coronary artery disease as well as with stroke in adults of European descent. Nevertheless such association has been found in black populations, where the concentration of Lp(a) is twice that of European whites[11,18,21].

Given the reported contribution of intrinsic factors, family history, and environmental factors related to the CVD risk in adults[22,23], the identification of inherited risk markers and environmental variables which may interact with levels of Lp(a) > 30 mg/dl (to mitigate the influence of developing atherosclerosis at an early age), is therefore imperative[3,19]. Few studies have examined the epidemiology of Lp(a) in representative samples of total populations of children and adolescents[24,25]. However, no study has examined whether the effects of inherited or acquired conditions or environmental factors interact with Lp(a) > 30 mg/dl, to cause differential attributable risk in different populations. The study of serum concentrations of this particle in children is especially important. Unlike LDL, Lp(a) concentration is postulated to be remarkably stable throughout the life of an individual[14]. Thus, identification of people at increased risk early in life would permit more effective intervention to lower levels of modifiable risk factors such as LDL cholesterol. In this sense, the aim of the present study is to determine Lp(a) concentrations in a sample of subjects from Maracaibo (aged from 5 to19 years old), as well as to find out the influence of family risk factors for cardiovascular disease on their Lp(a) levels.

Materials and methods

Study Population

The population included 369 school children and adolescents, between 5 and 19 years old (mean age 13.54 ± 0.21) of both genders and multi-ethnic composition. All of them participated in a voluntary survey for independent risk factors related to atherosclerosis in Maracaibo- Zulia State—Venezuela, over a two year period (2004-2005). All subjects were selected by means of random sampling in four schools and were evaluated at the Metabolic and Endocrine Research Center "Dr. Felix Gómez", at the Faculty of Medicine, University of Zulia. The study was presented to the school board of each school, afterwards a letter was sent to parents of all children and adolescents, which invited them to participate in the study, outlining the study goals and procedures. Parents were required to sign a written consent allowing participation of their children in the study. A detailed background clinical history (which included family history of heart disease, diabetes mellitus, hypertension, dyslipidemia and obesity) was carried out; a physical examination and laboratory test were performed to each patient in order to discard cardiovascular disease possibilities and confirm a healthy state. Height, weight, skinfolds thickness, waist circumference, and blood pressure measurements were carried out as well. Body mass index (BMI) was calculated (weight in kilograms divided by height in square meters) and children were defined as obese or undernourished on the basis of their BMI[26]. Individuals with positive clinical or biochemical findings for vascular, endocrine, liver or kidney disorders or any acute disease were excluded to avoid changes on Lp(a) serum levels based on the fact that this lipoprotein behaves as an acute phase reactant. A sample of 227 healthy children and adolescents was selected from the total population and were divided into three groups of age (5-9, 10-14 and 15-19 years old); the remaining group (142 subjects) defined as obese or undernourished on the basis of their BMI, or were positive for any of the formers disorders, or refused to sing the required informed consent, were excluded. The study protocol complied with Helsinki Declaration guidelines and was approved by the Ethics Committee of the "Dr. Félix Gómez" Research Center.

Lipoproteins and Lipids

Fasting venipuncture samples were drawn and were centrifuged within 30-45 min of collection. All blood lipids and lipoproteins analyses were undertaken at our research center. Seric Lp(a) concentration was measured using a double antibody ELISA method (HEBER Biotech, La Habana, Cuba). Triacylglycerols, total cholesterol and HDL-cholesterol were quantified by an enzymatic-colorimetric method (Human Gesellschaft für Biochemica und Diagnoses Mbh). VLDL and LDL-cholesterol was calculated using Friedewald`s formulas[27].

Statistical Analysis

All the statistical analyses were carried out using the SPSS software version 10.0 for Windows (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to evaluate Lp(a) distribution (Normal distribution or absence of Normal distribution). Since distribution turned out normal, results are shown as arithmetic mean ± standard error (EE). For inferential statistical analysis one factor ANOVA tests (post hoc Turkey test) and "t" student test for independent observations were used according to each case (considered significant when p value was <0.05).

The demographic and clinical characteristics of participants (134 girls and 93 boys) by gender are shown in table 1. Significant differences were observed between males and females for height, weight, BMI and Systolic blood pressure (SBP). The number of subjects by age group and gender is provided in table 2. The 227 individuals studied had a mean of 21.03 ± 1.10 mg/dl for Lp(a). No significant differences where observed when evaluating seric Lp(a) levels according to sex for all ages, having a 20.11 ± 1.29 mg/dl value for females and 22.34 ± 1.96 mg/dl for males (Table 3). Lp(a) levels for percentiles 50, 75 and 90 where 16.6, 27.2, and 37.4 mg/dl for females and 17.7, 30.7 and 53.4 mg/dl for males.

When male subjects were distributed according to age groups (with five year ranges), no significant differences were observed between groups in Lp(a) levels, although, in females a significant lower Lp(a) level in the group of 5-9 years (9.67 ± 2.53 mg/dl), was found when compared with groups of 10-14 (22.45 ± 2.04 mg/dl; p< 0.05) and 15-19 years (20.29 ± 1.69 mg/dl; p< 0.03). (Table 3). When Lp(a) levels were analyzed considering age but not sex, a significant lower level (p< 0.03) was observed in the 5-9 year old group (12.03 ± 3.22 mg/dl), compared with 10-14 (22.4 ± 1.67 mg/dl) and 15-19 year old groups (21.68 ± 1.59 mg/dl). (Table 3).

When the presence of family risk factors for CVD was studied (diabetes, hypertension, cerebrovascular disease, obesity, dyslipidemia and myocardial infarction); it was found that the group of subjects with at least one of those risk factors (n=152), had a significantly higher Lp(a) concentration (p<0.01) than those without it (n=75), (22.9 ± 1.0 mg/dl vs 17.2 ± 1.6 mg/dl). (Graphic 1A). Moreover, when the group with family risk factors for CVD was sub-divided by number of risk factors, it was evident that those with 4 or more risk factors exhibited a significant higher Lp(a) concentration than those with a lesser number of factors (30.6 ± 4.5 mg/dl vs 18.5 ± 2.2 mg/dl, p< 0.009 in those with 2-3 risk factors, and 21.6 ± 1.4 mg/dl, p< 0,03 in those with 1 risk factor) (Graphic 1B). No significant difference was found between the 2-3 risk factors group and the 1 risk factor group.

Table 1.Demographic and clinical characteristics of children and adolescents by genderArterial

	Boys (n=93)*	Girls(n=134)*	Total(n=227)*	*p*
Age (years)	13,91(0,32)	13,28 (0,28)	13,54 (0,21)	NS
Tanner stage	3	3	3	NS
Weight (Kg)	47,85 (1,76)	39,04 (1,61)	43,82 (1,24)	0,001
Height (m)	1,51 (0,02)	1,41 (0,02)	1,46 (0,01)	0,001
BMI (Kg/m2)	19,89 (0,37)	18,46 (0,33)	19,23 (0,25)	0,005
Fasting Glucose (mg/dl)	78,63 (0,94)	77,04 (0,83)	77,92 (0,64)	NS
Fasting Insulin (mU/ml)	12,80 (0,76)	14,23 (0,85)	13,44 (0,57)	NS
Total Cholesterol (mg/dl)	155,89 (3,17)	160,84 (2,98)	157,56 (2,21)	NS
HDL-cholesterol (mg/dl)	41,18 (0,89)	41,11 (1,06)	41,15 (0,68)	NS
LDL-cholesterol (mg/dl)	98,23 (2,83)	104,00 (2,85)	100,82 (2,02)	NS
VLDL-cholesterol (mg/dl)	16,88 (1,43)	16,79 (1,08)	16,84 (0,92)	NS
Triacylglycerides (mg/dl)	76,96 (3,23)	79,57 (3,37)	78,13 (2,33)	NS
Waist circumference (cm)	66,41 (1,16)	63,44 (1,13)	64,93 (0,81)	NS
Systolic blood pressure (mmHg)	100 (1,62)	95 (1,43)	98 (1,10)	0,01
Diastolic blood pressure (mmHg)	63 (1,31)	60 (1,15)	62 (0,88)	NS

*Mean ± Standard error (EE)
NS = no significant

Table 2. Groups of children and adolescents by age and gender

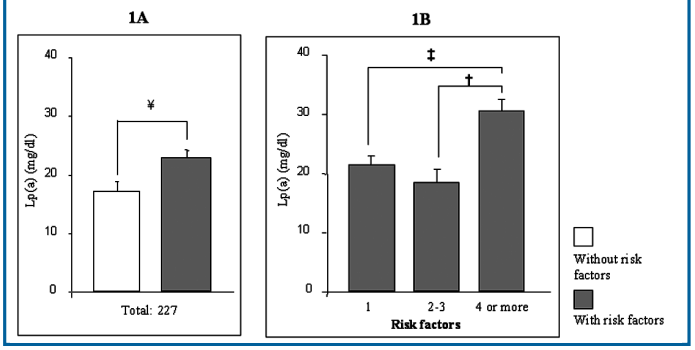
Groups	Boys	Girls	Total
5-9	7	16	23
10-14	42	68	110
15-19	44	50	94
Total	**93**	**134**	**227**

Table 3. Lp(a) serum levels in children and adolescents by age and sex

Groups(years old)	Girls (n=134)*	Boys (n=93)*	p	Total (n= 227)*
5-9	9.67 (2.53) c, d	17.45 (9.03)	NS	12.03 (3.22) a,b
10-14	22.45 (2.04) c	22.19 (2.90)	NS	22.40 (1.67) a
15-19	20.29 (1,69) d	23.26 (2.81)	NS	21.68 (1.59) b
Total	**20.11 (1.29)**	**22.34 (1.96)**	**NS**	**21.03 (1.10)**

* Mean ± Standard error (EE)
NS = no significant
p < 0.02 (a)
p < 0.03 (b, d)
p < 0.05 (c)

Graphic 1 . Lp(a) behavior in children and adolescents with and without family risk factors of coronary heart disease



¥ = p < 0.01
†= p < 0.009
‡ = p < 0.03

Discussion

The most significant findings of this study were:

First, Lp(a) levels tended to be considerably higher when the number of family risk factors for cardiovascular disease were four or more; second, Lp(a) levels were significantly higher between ages 10-19 in girls but not in boys, and third, the presence of age related differences in Lp(a) levels in the combined group. Moreover, the present work revealed no sex differences in mean Lp(a) concentrations, findings that are in agreement with the previous report from De Simone et al, who also found no significant changes with age[17]; however our results showed a significant lower Lp(a) level for the 5-9 years old female group.

There are numerous risk factors for CVD, whose presence in children greatly increases possible occurrence of the disease later on in mature life, for example, family history of diabetes, and family history of CVD, abnormalities in plasma lipoprotein levels, elevated levels of Lp(a), overweight or obesity and elevated blood pressure. At the present time, it is a well-known fact that atherosclerosis does not only affect elderly patients, but it starts as early as in childhood. Fatty streaks, the first lesion resulting in the development of atherosclerotic lamina may be observed even in the youngest children and its have been related with the presence of CVD risk factors[28,31].

In addition to the CVD risk factors formerly mentioned, in the last years more attention has been paid to Lp(a) as an independent risk factor of atherosclerosis. Elevated concentration of Lp(a) in adults have been associated with a higher risk of myocardial infarction, coronary heart disease, vein graft restenosis, and cerebrovascular disease, but elevated levels of Lp(a) are not only present in adult population, they can also be found in children and adolescents. Actually we found that 24% of the children and adolescents had Lp(a) concentrations above 30 mg/dl. One feasible explanation for this fact being reported up to now is that high Lp(a) concentrations, could be inherited and that they also closely correlate with the number of risk factors detected in the children's family history. This percentage is even higher in other studies, however the differences could probably be explained by the different methods used[17,32].

The preceding findings and the high mortality caused by circulatory system diseases motivated some researchers to numerically determine the occurrence and co-occurrence of risk factors in children and adolescents. It is recognized, though, that risk factors tend to cumulate in individual patients and significantly increases the possibility of being affected by the disease. The possibility of inheriting high Lp(a) concentrations, and its association with cardiovascular disease, may well explain that children with a positive parental history of CVD had a higher median Lp(a) value than did those with no relevant parental history[31].

When the presence of family risk factors for CVD in the 227 subjects was evaluated, we found that only 33% of the children and adolescents had no family risk factors for CVD, whereas the other 67% have from one to four or even more risk factors (35% have at least one, 16% have two or three and 16 % have four or more). The children and adolescents that had four or more family risk factors for CVD demonstrated significant higher Lp(a) levels than those children without the risk factors. This data is comparable with the one reported for Bailleul et al, who found in 2-year-old and 4-year-old French children that Lp(a) concentration directly correlates with the number of risk factors detected in the children's family history[32,33]. These results not only emphasize the importance of hereditary factors in high Lp(a), but also indicate that the evaluation of Lp(a) concentration should be taken into account as an independent risk factor for atherosclerosis in developmental age population. Children with burdened family history, with risk factors for atherosclerosis (obesity, dyslipidemia, diabetes, hypertension) and high Lp(a) level should be included in a special program for atherosclerosis prevention.

We conclude that this research represents a preliminary study that provides sex and age values for serum Lp(a) in children and adolescents in our population. Even though these results can not be taken as concluding data, they constitute an important report of Lp(a) levels in subjects between 5 and 19 years old and it is the first one that measured Lp(a) levels of children and adolescents in the region of Zulia-Venezuela. Furthermore, this study establishes the possible relation between Lp(a) levels and the number of risk factors for cardiovascular heart disease detected in the family history of the children –the greater the number of risk factors, the higher Lp(a) concentration-. To our knowledge, no such relationship has been previously reported in Venezuela. With this research we also emphasize the need to measure Lp(a) during childhood screening, especially when parents have risk factors for atherosclerotic disease. The detection of high concentrations of serum Lp(a) levels during childhood, signals the requirement to manage the atherosclerotic risk factors that can be modified by diet, lifestyle, and, in certain cases, with prescribed medicine.

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Preeclampsia-eclampsia

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Resumen

Los estados hipertensivos durante el embarazo (EHE) constituyen una de las tres primeras causas de muerte materna en nuestro país. Hasta el presente permanece desconocida su causa, razón por la cual los procedimientos empleados para su predicción, prevención y manejo son en gran parte empíricos.

Entre los EHE, el síndrome de preeclampsia-eclampsia (PE-E) tiene una incidencia que oscila entre el 3 y el 12% de las gestantes, dependiendo del área geográfica y la población estudiada. Generalmente aparece durante el 3º trimestre del embarazo, y su debut más temprano se asocia a un peor pronóstico.

Debe tenerse también en cuenta que esta patología contribuye con un altísimo porcentaje de la morbimortalidad perinatal, así como también su relación con un mayor riesgo de eventos cardiovasculares futuros en hijos de madres preeclámpticas.

En el presente trabajo se realiza una actualización de su epidemiología, modificaciones gravídicas en relación con el síndrome, y los últimos hallazgos conocidos en relación con su Etiopatogenia, a fin de ahondar sobre el problema, buscando acercarnos cada vez más a su predicción, prevención y manejo precoz una vez instaurado el cuadro, para mejorar las cifras de morbimortalidad materna y perinatal, entendiendo que se trata de una patología sistémica de origen multifactorial, para cuyo manejo se requiere la conformación de un equipo de salud multidisciplinario, pero además el concurso de la sociedad y el estado con el fin de optimizar las políticas sociales, económicas, educativas, ambientales, laborales, etc., de toda la población de la mayoría de nuestros países latinoamericanos.

Palabras claves: Preeclampsia - eclampsia; etiopatogenia; predicción; prevención.

Abstract

Hypertensive states during pregnancy (HSP) are one of the first three maternal causes of death in our country. We do not know the cause; thus the prediction, prevention and management are almost empiric.

Among HSP, the syndrome of preeclampsia has an incidence ranging between 3 and 12% of pregnant women, depending of the geographical and population studied.

Generally it appears during the third trimester of pregnancy and an early appearance is of reserved prognosis.

It is important to notice that this pathology contributes with high perinatal morbimortality, as well with the relation with greater risk of cardiovascular events in children of preeclamptic women.

In the present paper we updated the epidemiology, pregnant modifications in relation to the syndrome and recent findings with etiopathogenesis. The disease is of multifactorial origin and the management is multidisciplinary, in addition the health government to optimize social, economical, educative and laboral campaings.

Key words: Pre-eclampsia - eclampsia, etiopathogenesis, prediction, prevention.

Introduccion

Esta dramática y alarmante enfermedad recibe su nombre del griego "relámpago" o "brotar violentamente", cuadro extremadamente grave que puede presentarse durante el embarazo, el trabajo de parto, y en ocasiones en el postparto.

El papiro de Kahun (Petrie), que data de alrededor de 1850 años a.C, parece haber contenido cierta descripción de la enfermedad[1], cuando cita un artículo de F. L. Griffith (British Medical Journal, 1893) quien interpretaba dicho papiro de la siguiente manera: "para prevenir a una mujer de morderse su lengua un día después del parto…".

De acuerdo con Chesley[2], los griegos conocían ya de la existencia de la preeclampsia, manteniendo que Hipócrates (460-377 a.C) escribió en sus aforismos acerca del cuadro. Sin embargo, Adams[3], en su traducción dice: "resulta fatal para una mujer en estado de gestación si ella convulsiona con cualquier enfermedad aguda", lo cual amplía su relación no solo a la eclampsia.

Sostiene también Chesley[2], que Galeno, en el siglo II d. C., estaba de acuerdo con Hipócrates y comentaba que la epilepsia, apoplejía, convulsiones y tétanos, eran también mortales.

La literatura sobre la Eclampsia(E) comienza realmente con el advenimiento de las matronas varones en Francia (siglo XVII).

La preeclampsia (PE) no fue diferenciada de la epilepsia hasta 1739 por Sauveges. Demanet, en 1797, encontró anasarca en 6 pacientes eclámpticas. Lever y Simpson en 1843 encontraron proteinuria en pacientes eclámpticas (desaparecía en el posparto). Entre 1837-1867 la mortalidad materna por esa causa era del 30%, y a finales del siglo XIX se ubicaba en 24% (efecto de los anestésicos y la sedación con narcóticos).

atención del parto, razón por la cual, a partir de 1930, hubo gran interés en proporcionar mejor educación y formación de los profesionales sanitarios implicados en la atención de las gestantes.

La introducción de los cuidados prenatales se le atribuye a J. W. Ballantyne, en el Royal Maternity y Simpson Memorial Hospital de Edinburgh, en 1901.

La identificación de la patología prenatal y el diagnóstico precoz de la preeclampsia tuvo gran impacto sobre la mortalidad materna. Aunque se sabía de la existencia de la PE-E desde siglos atrás, fue John Charles Weaver Lever, en 1811 quien descubrió que la proteinuria se asociaba al cuadro. Alexander Henri Pillet, patólogo francés, fue quien demostró la relación existente entre eclampsia y cambios hepáticos hacia finales del siglo XIX. Los controles tensionales solo eran esporádicamente realizados incluso en 1915, razón por la cual el diagnóstico de la enfermedad era realizado tardíamente, alcanzándose las cifras de mortalidad hasta el 40%.

En la actualidad un 6-8% de los embarazos se ven complicados con estados hipertensivos, y aproximadamente un tercio de estas mujeres son finalmente diagnosticadas de PE.

Los estados hipertensivos constituyen una importante causa de morbi-mortalidad materna y perinatal; son responsables de un 15% de las muertes maternas y la primera causa de mortalidad fetal. Es necesario un abordaje multidisciplinario para el correcto manejo de estas pacientes.

La incidencia de PE es de un 3-12%, dependiendo del área geográfica y la población estudiada. Normalmente aparece durante el tercer trimestre del embarazo; un debut más temprano se asocia a un peor pronóstico.

En nuestro país constituye una de las tres primeras causas de mortalidad materna.

En una encuesta global realizada por la OMS entre 2004-2005 en Latinoamérica y África fueron encontrados los siguientes datos dependiendo de las variables buscadas:

	Región	
Variables	**Latino America n/N(%)**	**Africa n/N(%)**
Hipertensión	99/16096(0.62)	37/9162(0.40)
Crónica		
PreEclampsia	603/16097(3.75)	197/9163(2.15)
Eclampsia	23/16097(0.14)	27/9162(0.29)
Preeclampsia/Eclampsia (indicación de Inducción)	100/1513(6.61)	35/339(10.32)
Preeclampsia/Eclampsia (indicación de Cesárea)	498/5271(9.45)	81/912(8.88)

Países: Brasil, Nicaragua, Cuba, Perú, Paraguay, Ecuador, Argentina y Ecuador por Latino América; Argelia, Angola, Nigeria, Uganda, Nigeria y Kenya por África. Disponible en www.gfmer.ch/Educacion_medica_Es/Pdf/vienna

Epidemiología

Los índices de mortalidad materna han sido utilizados durante largo tiempo para la evaluación de la eficacia de los cuidados prenatales.

A principios del siglo XX esos índices se situaban en Europa y en América alrededor de 5 muertes por cada 100.000 nacimientos. Entre 1901 y 1905, en el Reino Unido era de 5,6, similar al de Australia. En EU fluctuó entre 7 y 9 por 1000, cifra muy elevada, similar a la del siglo XIX, razón por la cual se investigó su causa, encontrándose que era menor entre la población bien alimentada, multíparas que vivían en zonas rurales, a diferencias de las que lo hacían en ciudades y eran atendidas en hospitales, siendo ello prevenible hasta en dos tercios de los casos, y atribuible a falla en los cuidados prenatales y de un manejo inadecuado de la

En países desarrollados la preeclampsia es rara, afectando alrededor de 1 de cada 2.000 partos, mientras en los países en desarrollo esta cifra variará desde 1 en 100 a uno en 1.700[4,5].

De 600.000 mujeres que mueren mundialmente cada año por causas relacionadas con la preeclampsia, un 99% ocurren en los países en desarrollo, y la preeclampsia y la eclampsia son probablemente responsables directas de más de 50.000 de estas muertes[5,6,7]. Según la OMS (2004), en todo el mundo cada año:

- Más de 4.000.000 de mujeres desarrollarán PE
- Cerca de 100.000 mujeres presentarán convulsiones eclámpticas
- Más del 90 % de esos casos ocurrirán en países en desarrollo

Habrá de tenerse en cuenta que la patología en estudio contribuye además con un altísimo porcentaje de la morbimortalidad perinatal. Es reconocida la relevancia sobre el futuro de los hijos de madres preeclámpticas, quienes tienen un mayor riesgo de bajo peso al nacer, con las consecuencias que de ello derivan, así como futuro incremento de eventos cardiovasculares[8].

En relación al futuro materno, Smith et al[9] encontraron mayor riesgo de hospitalizaciones y muertes por enfermedad cardíaca isquémica entre las PE que tuvieron hijos de bajo peso.

Wilson et al[10],examinando la relación entre PE y riesgo de HTA y hemorragia cerebral, encontraron incremento de ambas, con aumento del riesgo relativo de 3,59 del accidente cerebrovascular.

Bar et al[11], siguiendo un grupo de embarazadas PE, y comparándolas con gestantes de evolución normal, encontraron que 2 a 4 meses después del parto, 2/3 de las PE presentaban microalbuminuria. Roest et al[12], sugieren que la microalbuminuria en postmenopáusicas constituye un factor de riesgo cardiovascular.

Según López Llera[13], "El análisis estadístico de la PE-E en nuestro medio es difícil por varios factores, entre los que resaltan el registro inadecuado de los casos, las diferencias de criterio diagnóstico entre hospitales, información incompleta o subregistro, y falta de uniformidad en los tratamientos utilizados; además de que el número de casos de PE-E ha aumentado en los últimos años no solo por crecimiento poblacional, sino también porque el problema está más presente en la conciencia del médico, propiciándose así un mayor número de internamientos. Con esto, el punto crucial es el grado de enfermedad con que llega la paciente, ya que por lo mismo es difícil determinar hasta dónde es reversible. No obstante queda la impresión que el índice de morbilidad no ha mejorado, y que no existe un consenso en cuanto a medidas de prevención, detección temprana y tratamiento oportuno".

Las adaptaciones cardiovasculares durante la gestación son requeridas para el logro de un adecuado aporte de oxígeno (O_2) y nutrientes a la placenta, y a su través, al feto. Estos cambios incluyen aumento de la volemia y el gasto cardíaco, y reducción de la resistencia vascular periférica, lo cual se correlaciona con un incremento en la producción de óxido nítrico (ON), al parecer debido al aumento del estrés de fricción y de los niveles circulantes de hormonas sexuales que ocurre durante el embarazo.

En algunas mujeres, la compensación a las variaciones fisiológicas del embarazo se resquebraja y ocurre la enfermedad multisistémica severa que los ginecoobstetras, nefrólogos, inmunólogos, cardiólogos, entre otros, conocemos como preeclampsia[14].

Endotelio

Conocido es que el endotelio constituye un tejido complejo y dinámico que ejerce importantes funciones en la pared vascular. Se le considera un órgano multifuncional que responde a estímulos muy disímiles: metabólicos, nerviosos, inmunológicos y mecánicos. Su funcionamiento depende de la integridad de sus células, de la interconexión entre ellas, y de la adecuada producción que realice de sustancias vasoactivas, elementos que le permiten desempeñar importante papel en variados procesos fisiológicos, tales como: interacción con las células blancas de la sangre, coagulación, fibrinolisis, agregación plaquetaria, angiogénesis, regulación del tono vascular, etc.

La realización de sus funciones la hace a través de la síntesis y liberación de sustancias paracrinas y autocrinas, tales como: prostaciclina, ON, factor hiperpolarizante derivado del endotelio (EDHF, por sus siglas en inglés), además de las endotelinas, y se pueden sintetizar en las siguientes actividades[15].

- Actuando como barrera macromolecular
- Proporcionando una superficie tromboresistente y fibrinolítica
- Regulando la función del músculo liso, para el mantenimiento del tono vascular y la PA
- Actuando como órgano antiaterogénico

Varios estudios han demostrado que en pacientes con HTA esencial se observa alteración de la función vasodilatadora del endotelio en relación con disminución de la bioactividad del ON, lo cual lleva a aumento de la resistencia vascular periférica, y por ende a HTA[16].

Ya iniciado el siglo XXI, continuamos desconociendo la etiología de la PE. Por los nuevos avances en la fisiopatología del proceso se ha llegado a la conclusión de que la denominación de Hipertensión Inducida por el Embarazo (HIE) usada durante la década anterior, no se ajusta a la realidad clínica.

Es bien sabido que la HTA es un signo importante del cuadro, al parecer consecuencia y no causa del mismo, considerándose que su papel es el de compensar la disminución del flujo placentario debido a la ausencia de los cambios que se suceden en el lecho vascular úteroplacentario durante el embarazo normal[17].

La PE ha sido definida como la "enfermedad de las teorías", debido a que hasta la actualidad ninguna de las propuestas ha podido explicar totalmente su origen y desarrollo.

Si bien la etiología de la PE permanece desconocida, en los últimos años se ha avanzado bastante en el conocimiento de los diferentes mecanismos involucrados en el proceso. Los descubiertos hasta el presente tienen como denominador común la disfunción endotelial (DE), entendida ésta como la pérdida de la capacidad del endotelio para modular el comportamiento fisiológico del lecho vascular, lo cual daría explicación a las distintas manifestaciones clínicas multiorgánicas que caracterizan la enfermedad.

El endotelio, funcionante o disfuncionante, ya sea en la vasculatura materna, de la placenta, o de ambos territorios, constituye elemento primordial en la determinación del curso fisiológico del embarazo, o en su desarrollo en condiciones de isquemia-hipoxia, con manifestaciones de PE, restricción de crecimiento intrauterino (RCIU), y parto pretérmino (PP)[18].

En la PE, las investigaciones actuales se orientan hacia la aclaratoria de cuál es la causa de la DE, centrándose la atención hacia la isquemia placentaria, el estrés oxidativo, la inadaptabilidad inmunológica, y los factores genéticos.

Numerosos hallazgos han sido encontrados y demostrados de manera constante en las pacientes PE, como la invasión citotrofoblástica endovascular insuficiente a las arterias espirales, la exagerada respuesta inflamatoria y la inadecuada activación de las células endoteliales, pero los mecanismos generadores de estos procesos permanecen hasta el presente desconocidos.

Hasta ahora, los mecanismos envueltos en la génesis de las modificaciones gravídicas cardiovasculares alteradas durante el síndrome de PE-E no están totalmente aclarados, pero se ha avanzado en los últimos años en el estudio de una serie de alteraciones que se correlacionan con dicho proceso. Así, ha sido demostrada baja concentración de calcio iónico sérico, lo cual ha sido atribuido a baja ingesta o inadecuada absorción intestinal del mineral[19].

También se ha reportado hipocalciuria en la embarazada PE[20].

Igualmente ha sido evidenciado que la PE es un cuadro que cursa con alteraciones de la placentación, las cuales se instauran desde etapas precoces de la gestación (1° trimestre), caracterizadas por la persistencia de la forma proliferativa del trofoblasto y la falta de cambio a una forma invasiva endovascular a nivel de las arterias espirales en su lecho decidual y luego intramiometrial, con conservación de la alta resistencia que genera incremento de la presión e hipoxia, lo cual se ha demostrado morfológicamente por endoteliosis placentaria, depósitos grasos similares a ateromas, y conservación de características vasculares similares a las preembarazo.

Incremento de óxido nítrico sintasa (NOS por sus siglas en inglés) en tejido placentario; de nitritos y nitratos en líquido amniótico y plasma o suero de algunas preeclámpticas, sugiere que el aumento de ON pudiera ser un mecanismo compensatorio más que un factor etiológico del cuadro[15].

En el síndrome de PE-E también ha sido involucrada la hiperhomocisteinemia (HHC), la cual se presenta en mujeres portadoras de una mutación del gen que codifica la enzima Cistatión β sintetasa (βCS), quienes presentan retardo mental precoz, luxación del cristalino, osteoporosis y escoliosis, trombosis y arterioesclerosis, y muestran niveles plasmáticos de homocisteína (HC) >100 µmol/L, y tasas de mortalidad del 50 % antes de los 30 años de edad[21].

La HHC se presenta debido a déficit nutricional o metabólico de las vitaminas B_6 y B_{12}; ácido fólico, y de la enzima metilentetrahidrofolato reductasa (MTHFR), flavoproteina que interviene en la remetilación de la HC. Esta se encarga de catalizar la reducción de la 5, 10 metilenetetrahidrofolato (5,10 MTHF) a 5, metilenetetrahidrofolato (5, MTHF), la forma más importante de folatos en el organismo, que actúa como cofactor donante de metilos para la remetilación de HC a metionina, lo cual es catalizado por la enzima metionina sintasa, y es dependiente de la Vit. B_{12}[22].

Al disminuir este cofactor, por déficit o alteración de la MTHFR, no se realiza la reacción de metilación de la HC, lo cual ocasiona aumento de su concentración plasmática, es decir, HHC.

Últimamente se ha definido la HHC como un factor de riesgo vascular independiente, asociándose a trombosis venosa profunda (TVP), arterioesclerosis, enfermedad coronaria y accidente cerebrovascular, describiéndose también su correlación con pérdidas gestacionales recurrentes, desprendimiento prematuro de placenta (DPP) y PE[23,24].

Entre los hallazgos encontrados en las investigaciones inmunológicas en relación con la PE, sobresalen los que relacionan la presencia de anticuerpos antifosfolípidos (AAF), con la presentación temprana y con graves complicaciones de la enfermedad[25].

En las preeclámpticas, al igual que en las gestantes afectas de infecciones diversas, se observa exceso de citoquinas proinflamatorias. Cuando fue instaurada antibioticoterapia en las pacientes con infecciones vaginales subclínicas y en infecciones del tracto urinario (ITU) se observó una disminución significativa (64,7%) de la tasa de PE esperada[26] lo que llevó a la hipótesis de que las infecciones subclínicas crónicas pueden aumentar la concentración de citoquinas proinflamatorias maternas capaces de afectar la función endotelial al crear un desbalance de $ON/O_2^{\cdot}$ con producción aumentada de radical libre peroxinitrito (ONNO), que es un poderoso oxidante, lo cual determinaría el posterior desarrollo de la enfermedad.

Un estudio elaborado por el Instituto de Investigaciones Biomédicas August Pi i Sunyer del Hospital Clínico de Barcelona y publicado en la revista científica AIDS ha demostrado que las mujeres embarazadas infectadas por el VIH tienen un riesgo ocho veces superior de sufrir preeclampsia y muerte fetal que las gestantes no infectadas. El riesgo aumenta cuanto mayor es el tiempo de infección y el de tratamiento con antirretrovirales previo a la gestación. En razón de tal circunstancia, se estima que toda gestante VIH + debe vigilarse de tal manera de poder realizarse un diagnóstico precoz de PE, a fin de evitar posibles complicaciones materno fetales.

También han sido involucrados en la fisiopatología de la PE-E innumerables compuestos, entre los cuales podríamos enumerar el Na, K, Mg, Zn, Se, y en la actualidad se evalúan en nuestro medio: "Actividades ATPásicas de Na y K en membranas plasmáticas de sincitiotrofoblasto en placentas de PE"; "Variaciones en los contenidos de calcio y magnesio en membranas plasmáticas y su posible relación con la disminución de la actividad ATPásica de calcio en fantasmas de glóbulos rojos de gestantes preeclámpticas"; y "Efecto de las hormonas tiroideas sobre la actividad de la ATPasa de Na, K de células del sincitiotrofoblasto" estos tres últimos trabajos tesis de grado de maestrías (2) y doctorado (1) UCV-IVIC.

Referente al estrés oxidativo, entendido éste como aquella situación en la que las células están expuestas a un ambiente prooxidante y los mecanismos defensivos antioxidantes son sobrepasados, de forma que se llega a afectar el estado redox (reacción de transferencia de electrones) celular. Para que exista una reacción redox (reacción de reducción-oxidación) en el sistema debe haber una especie que ceda electrones y otra especie que las acepte.

En los sistemas biológicos los elementos prooxidantes provienen en su mayoría del oxígeno, siendo denominados genéricamente especies reactivas de oxígeno (ROS).

Como ROS se incluyen a los radicales libres de oxígeno y a otros compuestos de oxígeno que, si bien no pueden catalogarse químicamente como radicales libres, son altamente prooxidantes y capaces de generar radicales libres durante su metabolismo. Un radical libre se puede definir como aquella especie química que posee un electrón desapareado. Esta situación le confiere una alta capacidad de reacción, prácticamente con cualquier principio activo, lo que también condiciona su corta existencia.

El radical libre que suele generar la existencia de las demás ROS es el anión superóxido. Su origen en la célula se sitúa en la mitocondria y en las membranas celulares. A partir del anión superóxido se forman el resto de ROS, destacando el peróxido de hidrógeno, peroxinitrito, hipoclorito y cloraminas, así como los radicales hidroxilo y dióxido de nitrógeno. Ante estos productos tan reactivos el organismo dispone de sistemas defensivos antioxidantes endógenos, con características enzimáticas o no.

Bioquímicamente en la PE se ha demostrado incremento en la producción de ROS; disminución de la actividad de citocromo C oxidasa a nivel mitocrondrial; aumento del activador del plasminógeno tipo 2; alteración de la producción del ON, y disminución de antioxidantes en el tejido placentario, y funcionalmente se ha evidenciado aumento de apoptosis en células placentarias; reacciones inmunológicas contra el trofoblasto; alteración en la diferenciación trofoblástica; disminución del número de arterias espirales invadidas e incremento de la respuesta a la angiotensina II de los vasos deciduales.

A pesar de que los casos de PE son esporádicos, es aceptado que factores genéticos juegan papel importante en su génesis. No obstante, su forma de herencia no sigue los modelos clásicos de herencia mendeliana.

Muchas investigaciones coinciden en que su origen se relaciona con la interacción entre factores genéticos y ambientales. Por esta razón, múltiples estudios han explorado los factores genéticos, tratando de identificar regiones cromosómicas y genes candidatos, cuyas variantes se relacionen con una mayor susceptibilidad a la enfermedad.

Inicialmente, algunos investigadores propusieron que la susceptibilidad podría ser heredada por un

gen único materno, autosómico recesivo, o por un gen dominante con penetrancia incompleta[27,28].

Múltiples investigaciones han demostrado que la enfermedad se presenta con agregación familiar, lo cual sustenta la evidencia de que tiene un componente genético importante[29,27,30].

Posteriormente se postuló que la susceptibilidad a la preeclampsia estaba condicionada por interacciones complejas entre dos o más genes maternos con factores ambientales, genotipos fetales y genotipos paternos (vía feto)[31].

Al reconocerse que la preeclampsia no está influenciada por un modelo genético materno exclusivo, se ha tratado de dilucidar el impacto de los genes fetales, encontrando que tanto madre como feto contribuyen igualmente al riesgo de preeclampsia; en este sentido, la contribución fetal estaría afectada también por genes paternos.

Seguimiento de familiares en primer grado de consanguinidad de pacientes PE ha demostrado que tienen 4 a 5 veces mayor riesgo de presentar la enfermedad, al igual que las de 2° presentan un incremento de riesgo de 2 a 3 veces, cuando se les compara con la población general[32,33].

Este tipo de predisposición familiar apoya la definición de PE como enfermedad compleja, donde los factores genéticos que contribuyen a su origen son múltiples, interactuando dos o más genes entre sí, herencia poligénica; o interactuando dos o más genes con diferentes factores medio ambientales, herencia multifactorial; donde la heterogenicidad genética del individuo determina distintas respuestas ante un factor externo.

Clasificación

Según el Séptimo Informe del Joint National Committee sobre Prevención, Detección y Tratamiento de la Hipertensión Arterial (JNC VII)[34], la clasificación aceptada actualmente para su estudio en adultos es la siguiente. Tabla 1

Tabla 1. Clasificación de la PA en adultos

CLASIFICACION PA	PAS (mmHg)	PAD (mmHg)
NORMAL	< 120	y < 80
Prehipertensión	120-139	ó 80-89
HTA: Estadio 1	140-159	ó 90-99
HTA: Estadio 2	> 160	ó > 100

El Consenso Latinoamericano sobre Hipertensión Arterial, elaborado dentro del marco de recomen-daciones del Comité Nacional Conjunto de Estados Unidos (US Joint National Committee, JNC) y la OMS-SIH, establece la siguiente Clasificación de la Hipertensión en el Embarazo Tabla 2[35].

Tabla 2. Clasificación de la hta en el embarazo

Categoría	PA≥140/90 Antes de 20 s	PA≥140/90 Después de 20s	Proteinuria	Pronóstico	Normotensa luego 12s del parto
HTA Crónica	Presente	Presente	Ausente	Según PA	Ausente
HTA Gestacional	Ausente	Presente	Ausente	Bueno	Presente
Preeclampsia	Ausente	Presente	Presente	Malo	Presente
PE + HTA Crónica	Presente	Presente	Presente	Malo	Ausente

Definiciones

HTA Crónica (HTA Cr.)

HTA de aparición previa al embarazo, o antes de la semana 20, o que persista después de las 6 semanas del parto. No se acompaña habitualmente de proteinuria, a menos que sea complicación de nefropatía.

HTA Gestacional (HTAG)

HTA de aparición posterior a las 20 semanas de gestación, con normalización durante las primeras 6 semanas del postparto, que no se acompaña de proteinuria.

Preeclampsia (PE)

Trastorno multisistémico específico del embarazo humano, de etiología desconocida hasta el presente, caracterizado por el desarrollo de hipertensión arterial (≥140/90 mmHg, paciente sentada, en reposo previo de al menos 5 minutos, y repetida al menos en dos oportunidades con intervalo mínimo de 4 horas) y proteinuria (>300 mg /24 horas o ≥ 2 + en muestra obtenida del chorro del medio, sin infección de vías urinarias), de aparición después de las 20 semanas de gestación.

Al parecer, se trata de una enfermedad de la placenta, debido a que se le observa también en embarazos donde hay trofoblasto sin tejido fetal (molas completas).

Hasta el presente a la PE se le sigue clasificando en Leve y Severa, aún cuando pensamos que ello conlleva a exceso de confianza en el manejo de la "leve", la cual puede pasar directamente a eclampsia (E), o a su complicación más temida, el Síndrome de Hellp, como veremos posteriormente.

La PE severa (PES) se caracteriza por presentar uno de los siguientes signos:

- AS >160 mmHg y/o PAD > 110 mmHg
- Proteinuria > 5 g/24 h, aún cuando algunos la consideran > 3 g/24 h; oliguria < 500 cc/24 h y elevación de la creatinina plasmática
- Edema agudo pulmonar
- Restricción del crecimiento intrauterino (RCIU).

Oligoamnios
- Alteración del funcionalismo hepático
- Dolor epigástrico o en hipocondrio derecho, debido a distensión de la cápsula de Glisson
- Trombocitopenia
- S. de Hellp

A pesar de que la PA es usada para el diagnóstico e índice de la progresión del cuadro clínico, se considera que la sintomatología, proteinuria, hallazgos de laboratorio y la presencia de disfunción orgánica, constituyen importantes indicadores de ello. Así mismo, pensamos que la sola buena evolución de las cifras tensionales no son garantía de buen pronóstico materno fetal, razón por la cual en ningún momento debe descuidarse la atención de la paciente.

Eclampsia

Se define como tal la aparición de convulsiones y/o coma en una mujer con gestación de más de 20 semanas de evolución con, o incluso sin clínica de PE, cuando aquellas no obedecen a otra causa. Se le considera una complicación de la PE.

HTA Cr. con PE sobreañadida (HTACr + PE)

HTA de aparición antes de las 20 semanas de gestación y/o persistencia de ella luego de las 6 semanas del postparto, o incremento brusco de ella a partir de esa edad gestacional, con presencia de proteinuria patológica.

Proteinuria

Definida como más de 300mg/día. Al reducir presión oncótica capilar puede favorecer la aparición de edemas.

Edemas

Definidos como acúmulo generalizado de líquidos luego de reposo durante 12 horas, o aumento de peso > 2,27 K/semana. Es un hallazgo común pero no incluido como criterio diagnóstico de PE.

El término de Hipertensión Inducida por el Embarazo (HIE) quedó abolido, debido a que se considera la HTA como una de las múltiples manifestaciones sistémicas de la PE-E, más no la única, lo cual señala el término de HIE, y además no se ajusta a la realidad clínica.

Así, es conocido que la HTA es un signo importante del cuadro, pero probable consecuencia y no causa del mismo, y pareciese que su papel es el de compensar la disminución del flujo placentario, debido a la ausencia de los cambios que se suceden en el lecho vascular úteroplacentario durante el embarazo normal[36].

Factores de riesgo (FR) de PE

Actualmente se considera la PE, más que como una enfermedad, un síndrome, cuyo origen, aún no bien determinado, se atribuye a diferentes causas. Para una mejor comprensión, sus factores de riesgo se clasifican en[37]:

- Genéticos o Hereditarios
  - Antecedentes personales de PE
  - Historia familiar de PE
- Maternos
  - Edad avanzada
  - Obesidad/Diabetes
  - Tabaquismo
  - Estrés/Trabajo forzado
  - Vasculopatías y nefropatías
  - Anticuerpos antifosfolípidos
  - Déficit de proteína S
  - Actividad de la proteína C
  - Hiperhomocisteinemia
- Inmunológicos
  - Tiempo de exposición al semen
  - Primiparidad
  - Adolescencia
  - Interciesis
  - Embarazos por inseminación artificial
  - Embarazos por donación de ovocitos
  - Padres de embarazos con PE
- Factores asociados a la gestación
  - Embarazo múltiple
  - Infección urinaria
  - Anomalías congénitas
  - Enfermedad trofoblástica

La mayoría de los factores de riesgo enumerados actúan como factores etiopatogénicos, razón por la cual no insistiremos más al respecto.

Muchos de ellos también constituyen FR de otras enfermedades endoteliales como la aterosclerosis y las complicaciones tardías de la diabetes mellitus (DM), al igual que se describe un menor riesgo de ellas en mujeres que no han presentado PE[38].

En cuanto a la edad materna, se ha vinculado la enfermedad con <25 y >35 años, y con la paridad, pero actualmente se establece una mayor relación con la duración de la cohabitación sexual previa como factor de riesgo importante[39].

El tabaquismo es considerado como factor vinculado con decremento en la incidencia de la PE. Se ha descrito una asociación protectora entre el tabaquismo y la PE, debido quizá a la actividad antioxidante.

El consumo del tabaco ocasiona efectos dañinos en muchos aspectos de la salud reproductiva de las mujeres y los hombres. Se ha asociado con placenta previa, desprendimiento prematuro normo placentario, embarazo ectópico y ruptura prematura de membranas, así como el ya descrito efecto protector de PE. Estos efectos se han tratado de explicar mediante varias teorías:

- El volumen plasmático se expande menos en embarazadas fumadoras que en no fumadoras[40].

- El tiocianato que se encuentra en el humo del tabaco tiene efecto hipotensor[41].

Factores predictivos (FP)

Han sido propuestos numerosos indicadores implicados en los cambios anatomopatológicos y en la fisiopatología de la PE, destinados a vaticinar su aparición posterior.

Hasta el presente no existe una prueba clínicamente útil, ni fieles indicadores bioquímicos y biofísicos para predecir su desarrollo. Es promisorio combinar marcadores de insuficiencia placentaria y de función endotelial, y los niveles séricos o urinarios del factor de crecimiento placentario (PlGF y sFlT-1) en el primer trimestre. Tan o más importante es la historia clínica personal y familiar de hipertensión.

Hasta el presente han sido planteados numerosos indicadores clínicos, bioquímicos y biofísicos para vaticinar la PE durante las etapas precoces del embarazo, sin que se haya conseguido alguna prueba única de tamizaje que sea confiable, válida y económica[42].

Se ha intentado identificar alteraciones capaces de predecir la placentación inadecuada, disminución de la perfusión, disfunción de las células endoteliales y activación de la coagulación, pero casi todos los intentos han resultado de baja sensibilidad para el pronóstico de la enfermedad.

Entre la metodología empleada que haya dado mejor resultado se encuentra la ecografía Doppler de las arterias uterinas entre las semanas 12 y 22; la detección temprana de signos de estrés oxidativo entre las 13 y las 21, y la disfunción endotelial desde edades precoces del embarazo.

En la actualidad evaluamos en nuestro servicio, como predictor de PE durante el final del 1º e inicios del 2º trimestre, la hiperemia reactiva en la arteria braquial de madres para el momento normales, lo cual ha sido estudiado en relación con la afección endotelial en hipertensos, con buenos resultados como predictor[43].

Igualmente hemos comparado la proteinuria en 24 horas vs la misma en 12 horas nocturnas, encontrando una muy buena correlación entre ambas[44].

Algunos trabajos sugieren que la hiperuricemia participa en el desarrollo de la hipertensión y del síndrome preeclámptico[45].

Se debe principalmente a la disminución de la excreción renal por disminución de la filtración glomerular[46].

Así mismo puede haber una producción excesiva de ácido úrico por la placenta isquémica[47].

Está bien definido que la concentración de ácido úrico constituye un marcador importante en pacientes con preeclampsia, pero es poco probable que tenga uso considerable como predictor de la enfermedad, pareciendo que se correlaciona es con la evolución del cuadro[48,49].

Igualmente se ha propuesto como FP la infusión de Angiotensina II, difícil de realizar en la práctica clínica; la prueba de la rotación, con un valor predictivo positivo del 33%; las alteraciones del metabolismo del Ca, con sensibilidad para la predicción de PE del 88% y valor predictivo positivo del 32%; la excreción de calicreína, con valor predictivo positivo no confirmado[50]; los niveles plasmáticos de fibronectina, con baja sensibilidad (69%) y de valor predictivo positivo (12%).

Así mismo, la trombocitopenia y las anomalías de la función plaquetaria (agregación), como test de activación de la coagulación, han sido planteados como posibles buenos indicadores de la DE; algunos indicadores de estrés oxidativo, como la peroxidación de lípidos malondialdehídicos, diferentes prooxidantes o potenciadotes de prooxidantes como hierro; homocisteína; lípidos sanguíneos como triglicéridos, ácidos grasos libres y lipoproteínas, y antioxidantes como el ácido ascórbico y la vitamina E han sido evaluados también como tales.

Algunos péptidos placentarios como la hormona liberadora de corticotrofina, la gonadotropina coriónica, la activina A y la inhibina A, al parecer, pudieran ser buenos indicadores predictivos del síndrome PE[51].

Complicaciones

Las complicaciones del síndrome de PE se presentan con mayor frecuencia en su forma grave, lo cual no descarta que en la catalogada como leve no puedan aparecer. Es así como hemos visto en la práctica diaria gestantes convulsionando con una PA ≤140/90 mm Hg., desencadenando posteriormente el cuadro típico de una eclampsia, o en ocasiones de un S. HELLP.

Para una mejor comprensión, desde el punto de vista didáctico, podríamos clasificarlas en:

- Maternas
  - Eclampsia
  - Síndrome de HELLP
  - DPPNI
  - Insuficiencia renal
  - Rotura hepática
  - CID
  - Hipertensión crónica (secuela)
- Fetales
  - RCI
  - Sufrimiento fetal
  - Óbito
  - Inmadurez, prematurez

Brevemente trataremos en forma sucinta las complicaciones más graves, causas de alta morbimortalidad materna y perinatal.

Eclampsia

Como tal se denomina la PE que se complica con convulsiones tónico-clónicas generalizadas. Aparece casi siempre precedida por el cuadro sindromático de la PE, aproximadamente en un 50-60% durante el embarazo, generalmente durante el último tercio del 3º trimestre, siendo de peor pronóstico en edades gestacionales precoces; un 15 a 20% durante el trabajo de parto y el resto durante el puerperio inmediato, aún cuando se describen casos de aparición hasta el 10º día del puerperio.

Aún cuando su patogenia no está del todo aclarada, se cree debida a hipoxia cerebral severa y/o a pequeñas hemorragias peri capilares cerebrales producidas como consecuencia del severo vaso espasmo que ocurre en la PE, o a encefalopatía hipertensiva con hiperperfusión, edema vasógeno y daño endotelial[52].

Constituye uno de los cuadros más graves de la patología obstétrica, y produce una alta tasa de mortalidad materna debida generalmente a hemorragia cerebral.

El ataque eclámptico se antecede generalmente de epigastralgia, cambios de carácter, cefalea intensa, e incremento notable de las cifras tensionales.

Luego del estado convulsivo se establece un estado de obnubilación o coma, premonitorio de nuevas convulsiones o muerte. En ocasiones la paciente queda posteriormente con amaurosis.

Anteriormente se le consideraba como etapa siguiente de la PE, de allí su nombre, pero hoy se sabe que las convulsiones constituyen una de las manifestaciones clínicas de la PES.

El diagnóstico diferencial de las convulsiones eclámpticas hay que plantearlo con las siguientes entidades: Epilepsia; encefalitis; meningitis; tumor cerebral; cisticercosis; ruptura de aneurisma intracraneano; intoxicaciones medicamentosas, etc.

Respecto a su pronóstico, se ha descrito la ocurrencia de complicaciones maternas hasta en el 70% de las eclámpticas, tales como: CID, insuficiencia renal aguda, rotura hepática, lesión hepatocelular, hemorragia intracerebral, isquemia cerebral, paro cardiorrespiratorio, neumonitis por aspiración, edema pulmonar agudo. La tasa de mortalidad materna oscila entre 0 y 13.9%, y en un subgrupo de gestantes con eclampsia antes de las 28 semanas alcanzó el 22%. Estas altas tasas de mortalidad bajan significativamente con una atención prenatal precoz, regular y de buena calidad, y, por supuesto en un medio apropiado.

Síndrome HELLP

Complicación grave de la PE descrita inicialmente por Pritchard en 1954[52], aún cuando el nombre de HELLP fue dado por Weinstein en 1982[54].

Su nombre está dado por el acrónimo formado por las iniciales en inglés de los datos de laboratorio que lo caracterizan: Hemolysis, Elevated Liver function tests and Low Platelets count.

Se ha descrito la presencia de una de las anomalías descritas en el 6% de las PES (generalmente alteraciones de la función hepática o trombocitopenia); 12% de dos de ellas y alrededor del 10% de tres[55].

Los criterios de laboratorio para su diagnóstico más utilizados[55] son:

- Hemólisis, determinada por la presencia de esquistocitos en sangre periférica
- Bilirrubinemia total > 1.2 mg/dl
- Aumento de enzimas hepáticas: Aminotransferasa de aspartato > 70 U/L; LDH > 600 U/L
- Trombocitopenia < 100.000 / mm^3

Con base a estos criterios, los investigadores de Memphis[56], han propuesto su clasificación en completo y parcial o incompleto, según presentara todos los criterios descritos anteriormente (completo) o con al menos uno de ellos (parcial). A esta se le conoce como clasificación de Tenneessee.

Martin y colaboradores[56], lo clasifican en tres clases:

Clase 1, con trombocitopenia ≤ 50.000 / mm^3

Clase 2, trombocitopenia entre >50.000 y ≤100.000 / mm^3

Clase 3, trombocitopenia > 100.000 y ≤ 150.000 / mm^3

Es conocida como clasificación de Mississippi.

La presencia del S. HELLP está asociada a un mayor riesgo de muerte materna (1%) y aumento de morbilidad materna: edema pulmonar agudo (8%); insuficiencia renal aguda (3%); CID (15%); desprendimiento prematuro normo placentario, síndrome de dificultad respiratoria del adulto, sepsis, etc. El riesgo de recurrencia en embarazos posteriores ha sido descrita entre un 3 a un 27%. El riesgo global de complicaciones en el S. HELLP oscila entre el 19 y el 43%[58].

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Homeostasis model assessment (HOMA) as surrogate insulinization criteria in patients with type 2 diabetes

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Abstract

Objectives

Type 2 diabetes mellitus is a metabolic disorder that results from defects in both insulin secretion and insulin action. Questions remain about when insulin therapy must be indicated, thus the aim of this study was to evaluate $HOMA_{\beta cell}$ as surrogate criteria for insulin therapy indication in patients with type 2 diabetes.

Subjects And Methods

A prospective study was performed in 189 type 2 diabetic patients with deficient metabolic control assessed by clinical and laboratory parameters. All patients received nutritional intervention and combination therapy with Metformin and Glimepiride. Patients that did not respond were admitted to the next phase, which consisted in Glimepiride+Metformin+Rosiglitazone oral therapy and then, revaluated after 3 months. Comparisons between responders and non-responders in this phase were made in order to achieve differences in metabolic parameters and βcell function.

Results

Out of 189 patients studied, 150 (79,36%) were considered as fully responders in the first phase of this study. The remaining 39 patients were admitted in the second trial phase in which 20 patients (51,28%) responded to triple oral therapy, while the other 19 (49,72%) required insulin therapy. Significant differences were found in fasting and post-pandrial glycemia ($p<0,001$; $p<0,004$) between the non-insulin requiring group (200±12,0 mg/dl; 266,05±17,67 mg/dl) and the insulin-requiring group (291,5±17,6 mg/dl; 361,6±26,1 mg/dl). Likewise, significant differences were observed in $HOMA_{IR}$ and $HOMA_{\beta cell}$ ($p<0,002$; $p<0,04$) between non-insulin requiring patients (7,7±0,8; 24,5±1,3%) vs. insulin-requiring patients (12,6±1,2; 19,4±2,4%). Finally, significant differences were observed when comparing body mass index (non-insulin requiring group 29,2±0,4 Kg/mt^2 vs. insulin-requiring group 27,1±0,9 Kg/mt^2; $p<0,05$).

Conclusions

$HOMA_{\beta cell}$ determination in the clinical practice is a useful tool to assess when insulin therapy should be started type 2 diabetic patients.

Key words: HOMA, insulin, type 2 diabetes.

Introduction

According to data published by the World Health Organization (WHO) in 2006, more than 180 million people worldwide have Diabetes and by the year 2030, this number probably will experience a two-fold increase[1]. Type 2 Diabetes Mellitus (DM-2) has become a major worldwide public health problem, but is more common in developed countries[2,3]. By 2025, the countries with the largest number of peo-

ple with DM-2 will be India (> 57 million; prevalence 6%), China (> 37 million; prevalence 3.4%), and the United States (> 21 million; prevalence 8.9%). Currently, over 17 million Americans have been diagnosed with diabetes, and 5.9 million are unaware that they even have the disease. Based on prevalence rates predicted from 1980-1998 trends, the number with diagnosed diabetes in the United States will swell to 29 million by 2050[4]. The increasing incidence of diabetes in developing countries follows the trend of urbanization and "Westernized life style"[5], suggesting an important environmental effect in interaction with genetic factors responsible for peripheral insulin resistance and secondary βcell dysfunction[6,7].

Resistance to peripheral insulin action is due to multiple mechanisms and the intimate molecular basis have been described elegantly by a number of investigators like Randle and more recently by Shulman et al, highlighting that an increase in serum free fatty acids (FFA) are typically associated with insulin-resistant states[8,9,10]. These compounds compete with glucose for substrate oxidation in muscle cells abolishing insulin-stimulated IRS-1–associated PI 3-kinase activity probably through protein kinase C activation that results in a fall in glucose transport by Glut-4 in muscle cells and adipocytes[8,11].

Therapeutic intervention in DM-2 aims β-cell function preservation by direct gluco-lypotoxicity management, peripheral insulin resistance control and rational nutritional approach, allowing a higher glucose uptake in peripheral tissues[12,13,14,15]. Thus, insulin and secretagogues like sulfonylureas, have been indicated in those patients in whom sensitizing agents monotherapy does not improve overall glucose control[16,17]. Despite its benefits, the use of these drugs could drive to secondary β-cell exhausting[18]. It is estimated that by every year of sulfonylurea treatment 5% of patients present secondary pancreatic failure and thereby lack to obtain a suitable metabolic control regardless of fulfilling nutritional maneuvers, accomplishing physical activity and pharmacological treatment[19,20]. Pancreatic failure is demonstrated by permanently elevated glucose levels and an increase of advanced glycosylation end products outpost like HbA1c, which make part of the clinical guidelines of insulin therapy in patients with DM-2[21,22].

The United Kingdom Prospective Diabetes Study (UKPDS), demonstrated that the percentage of sulfonylurea treatment associated with a secondary response failure (1,395 patients) was of 44% within the 6th year of use with an annual rate of 7.3%[23]. By the 10th year of evolution, 70% of type 2 diabetic patients needed treatment with insulin alone or in combination with any of the oral agents[23].

To determine only by clinical parameters accurately when insulin therapy should be required is in most cases difficult in terms of time required to wait in order to obtain an adequate metabolic response, meanwhile glycosylation, glucotoxicity, lipotoxicity, and atherosclerosis are damaging patient's tissues and organs[10,15,24,]. In most cases, commonly used criteria appear so late in disease evolution that β-cell function is already deeply deteriorated, and thus, functional recovery probabilities are reduced[21,25]. This fact frequently leads to either unnecessary delayed insulin therapy instauration or precocious therapy with this hormone[26,27,28,29].

Since to date there is not a consensus regarding to an optimal timing for insulin treatment initiation (early vs. delayed)[28,29] and many clinical trials have been carried out by relying on the above mentioned clinical criteria without taking into account the pancreatic secretory reserve[21,30], in consequence, the aim of this study was to evaluate pancreatic insulin secretory function in individuals with long-term DM-2 and lack of metabolic control, in order to establish the existence of insulin secretory capacity differences measured through the Homeostasis Model Assessment β-cell (HOMA β-cell)[31] in patients selected for insulinization by the classical clinical criteria compared to patients under the same clinical circumstances that achieved clinical response with double or triple oral combination therapy (Glymepiride, Metformin, and Rosiglitazone)[10,28,29,32-34].

Subjects and methods

Subjects' selection

A prospective study was performed in which 189 Hispanic whites of both sexes, type 2 diabetic patients diagnosed according to the American Diabetes Association criteria, were included. The patients were recruited from the diabetes consult at the Endocrine and Metabolic Diseases Research Center "Dr. Félix Gómez" (Centro de Investigaciones Endocrino-Metabólicas "Dr. Félix Gómez"), School of Medicine, University of Zulia, Maracaibo, Venezuela.

Patients enrolled in the study were selected according to the following inclusion criteria:

a) Ages between 40 and 60 years.

b) Long-term type 2 diabetes (>10 years of evolution since diagnosis).

c) Long standing lack of metabolic control, despite accomplishing nutritional and pharmacological monotherapy treatment defined by: Hb1Ac > 10 %, fasting glycemia >180 mg/dl and post-pandrial glycemia > 240 mg/dl for more of four consecutive months.

d) Or patients with previous irregular pharmacological treatment based on sulfonylurea monotherapy or individuals with DM-2 who had never accomplished nor pharmacological or nutritional therapy as treatment and presented metabolic parameters as indicated in A, B and C.

e) Individuals with previous history of MODY, gesta-

tional diabetes or other pathologies that could cause hyperglycemia (thyroid disease, Cushing's disease, chronic pancreatitis and corticosteroids treatment) were excluded of this study.

Study design

All selected patient underwent fasting and 2 hour venous blood sample collection in order to determine fasting glycemia (glucose-oxidase colorimetric method; HUMAN, Germany) and fasting insulin (solid phase radioimmunoassay, DPC, USA), glycated A1c hemoglobin (HbA1c, cationic exchange resin separation method, SIGMA USA) and post-pandrial glycemia, before pharmacological treatment was administered.

In order to corroborate lack of response to treatment, each patient was submitted to nutritional intervention according to ADA guidelines and to an initial two-drug combination therapy consisting in Metformin (Glucofage, Merck, Germany) 500 – 850 mg with each meal plus Glimepiride (Amaryl, Aventis Pharma, Germany) 2–4mg before breakfast. The follow up period was of 3 months. Patients who reached an euglycemic state defined by fasting and post-pandrial glucose and HbA1c levels normalization were considered as responsive and were not admitted into the next phase of the study. Patients that did not respond were admitted to the next phase, where Rosiglitazone was administered at a dose of 8 mg daily (GlaxoSmithKline, UK) and then, revaluated after 3 months. Fully responding patients were closely monitored and maintained with a triple oral antidiabetic therapy, and the non-responding patients were placed on insulin therapy at 0,5 – 1 U/kg of body weight per day with weekly adjustments according to basal and postprandial glucose levels.

Comparisons between responding and non-responding patients in the second phase were made in order to achieve differences in the metabolic parameter behavior and β-cell function patterns, previous to final treatment allocation.

Insulin resistance and β-cell functionalism calculation

To derive estimates of β-cell function and insulin resistance, the formulas from the Homeostasis Model Assessment (HOMA) were applied:

- Insulin resistance:

$$\text{HOMA IR} = \frac{\text{Fasting insulin (µIU/ml) x fasting glucose (mmol/L)}}{22.5}$$

- β-cell function:

$$\text{HOMA β-cell} = \frac{\text{Fasting insulin (µIU/ml) x 20}}{\text{Fasting glucose (mmol/L)} - 3{,}5}$$

Statistical Analysis

All data was analyzed by SPSS 13.0 for Windows. Normality (or not) variable distribution was assessed by Kolmogorov-Smirnov test. Results were expressed as arithmetic mean ± standard error. Differences between means were assessed using unpaired Student's t-test, considering as significant when the value of $p < 0.05$.

Results

Studied patients

Out of 189 patients studied, 150 (79,36%) were considered as fully responders when double oral therapy (Metformin plus Glimepiride) was initiated during the first phase of this study. These individuals achieved and maintained an euglycemic state during all follow-up study period (6 month). The remaining 39 patients were admitted in the second trial phase in order to receive triple oral agent combination (Glymepiride + Metformin + Rosiglitazone), out of which 20 patients (51,28%) responded to therapy, while the remaining 19 (49,72%) required insulin therapy. Overall, 94 % of the patients with clinical insulinization criteria achieved an optimal metabolic control with only nutritional maneuvers, physical activity and dual or triple oral antidiabetic combination therapy.

General data and metabolic parameters in patients admitted to second study phase

Age, evolution time since diagnosis and body mass index

No significant differences were observed between responders and non-responders patients when comparing age (non-insulin requiring group 58,3 ± 1,9 years vs. insulin requiring group 54,6 ± 1,7 years) and disease evolution since diagnosis (non-insulin requiring group 11,2 ± 1,5 years vs. insulin requiring group 11,7 ± 2,2 years). A significant difference was observed when comparing body mass index (non-insulin requiring group 29,2 ± 0,4 Kg/mt^2 vs. insulin requiring group 27,2 ± 1,0 Kg/mt^2; $p<0{,}05$). Table 1.

Table 1. Clinic and biochemical patterns in responders and non-responders patients with type-2 diabetes mellitus enrolled in the second study phase

	Responders(n=20)	Non-Responders(n=19)	*p*
Age	58,4 ± 1,9	54,6 ± 1,8	NS
Disease evolution since diagnosis (years)	11,2 ± 1,5	11,8 ± 2,3	NS
BMI (kg/m2)	29,2 ± 0,4	27,2 ± 1,0	<0,05
Fasting Glycemia (mg/dl)	200,4 ± 12,0	291,6 ± 17,6	<0,001
Post-pandrial Glycemia (mg/dl)	266,1 ± 17,7	361,7 ± 26,1	<0,004
Fasting Insulin (uU/ml)	15,1 ± 0,9	17,6 ± 1,3	NS
Post-pandrial Insulin (uU/ml)	39,6 ± 1,7	40,2 ± 3,9	NS
HbA1C (%)	9,6 ± 0,3	10,0 ± 0,2	NS
HOMA-IR	7,8 ± 0,8	12,6 ± 1,2	<0,002
HOMA-b-cell (%)	24,5 ± 1,3	19,5 ± 2,1	<0,04

BMI: Body mass index HbA1c: Glycated Hemoglobin NS: non-significative

Fasting and post-pandrial glucose behavior

Fasting glycemia: Significant differences were found (p<0,001) between the non-insulin requiring group (200 ± 12,0 mg/dl) and the insulin-requiring group (291,5 ± 17,6 mg/dl). Figure 1, table 1.

Post-pandrial glycemia: When comparing the non-insulin requiring group (266,05 ± 17,67 mg/dl) with the insulin requiring group (361,6 ± 26,1 mg/dl), significant differences were observed (p<0,004). Figure 1, table 1.

Fasting and post-pandrial insulin levels

No significant differences were found related to fasting insulin levels (non-insulin requiring group: 15,1 ± 0,8 µIU/ml Vs insulin requiring group 17,5 ± 1,3 µIU/ml), and neither were significant differences found when comparing post-pandrial insulin levels (non-insulin requiring group: 39,6 ± 1,7 µIU/m Vs insulin requiring group 40,2 ± 3,8 µIU/ml), p = 0,1. Figure 1, table 1.

Glycated hemoglobin levels (HbA1C)

No significant differences were seen when comparing HbA1c levels between the non-insulin requiring (10,5 ± 0,3%) Vs. the insulin requiring group (12,6 ± 1,2%), p = 0,08. Table 1.

$HOMA_{IR}$ and $HOMA_{\beta cell}$ Determination

HOMA-IR: Significant differences were observed (p<0,002) between non-insulin requiring patients (7,7 ± 0,8) vs. insulin requiring patients (12,6 ± 1,2). Figure 1, table 1.

HOMA β-cell: Significant differences were found (p<0,04) when comparing non-insulin requiring patients (24,5 ± 1,3 %) vs. insulin requiring patients (19,4 % ± 2,4). Figure 1, table 1.

Discussion

DM is a serious and chronic metabolic disease with multiple complications and premature mortality, accounting for at least 10% of total health care expenditure in many countries[3,35]. According to the 2004 data from the WHO, more than 150 million people around the world suffer from diabetes and projections estimate a further doubling in the first 25 years of the new millennium[36,37]. However, the greatest increases in DM prevalence rates will be in developing nations such as Asia and Africa, where most of the diabetic patients will be diagnosed by 2025 [37]. The increase of diabetes mellitus incidence in developing countries follows the trend of urbanization and changes in lifestyle patterns and diet[5,36]. Probably, the dramatic occurrence of DM will likely continue because of the growing prevalence of obesity[5,38].

Insulin resistance (IR), the leading abnormality in patients with DM-2 is characterized by the incapacity of insulin-sensitive tissues to respond to normal insulin circulating levels[8,30]. Thus, in order to offset IR, pancreatic β-cells increase its insulin production and secretion. However, over time β-cell function deteriorates, less insulin is secreted, and hyperglycemia develops. In conclusion, DM-2 must be seen as a result of two main alterations: 1) peripheral IR which leads to both, hepatic fasting glucose over-production and post-pandrial muscle glucose uptake inhibition, and 2) secondary drop in insulin production via β-cell secretory dysfunction and apoptosis[25,39,40].

During DM-2 evolution, alterations in insulin secretory patterns (blunted first-phase insulin release) begin more than a decade before the disease is even diagnosed. Indeed, it is already present in normoglycemic first-degree relatives of DM-2 patients and people with impaired fasting glucose as a result of a complex interplay of genes and environment[6]. Hyperglycemia and free fatty acids behave as β-cell stressors acting via ceramide synthesis. This, in turn activates nitric oxide synthase expression, increasing nitric oxide concentrations and accelerating cellular apoptosis [25,39,40,41]. In addition, free fatty acids may suppress the expression of genes responsible for stem cell formation in the pancreatic ducts. However, a recent study showed that apoptosis, rather than decreased β-cell formation, is the key event involved in the β-cell mass lost seen in DM-2[25,40]. Therefore, the impact of pharmacological options on β-cells survival should be considered in order to improve the overall DM-2 control. In this sense, some studies conducted with tolbutamide and glyburide, have shown to activate apoptosis in β-cell lines and rodent islets, as well as in cultured human islets[42]; by contrast, both nateglinide and repaglinide and thiazolidinediones (rosiglitazone or pioglitazone) have a markedly positive effect on β-cell survival[43]. In adittion, a recent study conducted by our group in type 2 diabetic individuals with a mean of 7 years of evolution since diagnosis and 50% β-cell reserve measured by $HOMA_{\beta\text{-cell}}$, showed a full recovery of pancreatic secretory capacity in the three intervention groups (diet alone, Metformin monotherapy and Glymepiride and Metfomin dual therapy)[44]. Since metabolic disorders responsible for DM-2 coexist in the same individual, that is, muscle insulin resistance, hepatic insulin resistance and β-cell secretory dysfunction, we suggest that treatment should be reoriented to pharmacological management of those 3 conditions, altogether with a nutritional plan and physical activity that will promote weight loss in patients with overweight and obesity, diminishing free fatty acid offer to liver and muscle, avoiding insulin resistance in these tissues[14].

It is interesting how this study design included patients with clinical insulinization criteria due to the

lack of response to oral therapy; however, it is even more impressive how these patients responded to double or triple-combination therapy with oral agents, that is, the addition of two sensitizers drugs such as Metformin[10] (mayor effect on liver) and Rosiglitazone (mayor effect on muscle and adipose tissue)[33,45]. The fact that 94% of all patients responded with normalized glycemic control parameters could be due to several elements. First of all, the responders group was in average younger and less insulin resistant than the non-responders group. Moreover, it is possible that the clinical criteria used til' now lacks sensitivity and specificity enough to select accurately patients in which insulin therapy should be started immediately, and thus, many patients labeled as "insulin-requiring" are probably not[28,29]. And second, monotherapy with oral agents, just as the UKPDS study points out, does not help accomplish euglycemic states for long periods of time, which is why a great deal of studies support moving on to combination therapy with oral agents in those individuals that do not respond to monotherapy[16].

On the other hand, some authors propose early insulin administration as an alternative approach that may provide "β-cell rest" and some degree of protection from apoptosis[17,46]. Moreover, according to observational and interventional evidence, insulin therapy may preserve endothelial function and help to achieve a better glycemic control diminishing all retinopathy, progression of preexisting retinopathy, incidence of diabetic nephropathy and progression of diabetic neuropathy[24]. Despite of this data, insulin treatment may have a dark face in DM-2 management. For instance, in the Veterans Affairs Cooperative Study in Type II Diabetes (VACSDM) 153 men with long-standing diabetes were randomly assigned to receive either standard insulin treatment (one morning injection daily) or intensive therapy combining dietary education and blood glucose self-monitoring[47]. After 6 months, the mean HbA1c in the intensive therapy group was at or below 7.3% and remained 2% lower than the standard group for the duration of the trial, but there were 61 cardiovascular events in 40 patients and 10 deaths (6 due to cardiovascular causes) a higher number than expected for this group of patients.

In this framework, it is vital to clarify when a diabetic patient faces a non-return point in which β-cell function becomes irrecoverable or at least not sufficient enough to maintain a long lasting euglycemic state. All the above mentioned explains partially why insulin therapy initiation in DM-2 has stimulated scientific debate over the last five decades[29].

In our study, a statistical significant difference was found when comparing basal and post-pandrial glucose levels among non-insulin requiring type 2 diabetic patients and those that required initial insulin therapy. Likewise, a significant difference was observed when comparing the degree of insulin resistance measured by $HOMA_{IR}$ between non-insulin requiring type 2 diabetic patients and those that required initial insulin therapy in favor of the latter group. In this case, It is plausible that insulin resistance phenomena represents a heterogeneous entity affecting in a different degree the metabolic control in each patient, and in consequence, its role as pancreatic stressor may vary beetwen each individual as its seen in both studied groups. Nevertheless, environmental and other genetic factors are not to be excluded as important inter-players in the final metabolic response caracterized by hepatic glucose over production and altered glucose uptake by muscle following insulin receptor down-regulation and glucose transporters (GLUT-4) internalization[11-21].

Beta-cell vulnerability is strongly bounded to both genetic and environmental factors that could account for individual differences[7], however, other factors such as free fatty acids and Resistin could also trigger transitory and permanent functional changes in β-cell secretory capacity[10,48]. When comparing pancreatic β-cell function between the non-insulin requiring vs. insulin requiring patients, average $HOMA_{\beta cell}$ was statistically superior for the non-insulin requiring group than the insulin requiring group. This finding suggest that those patients with $HOMA_{\beta cell}$ values under 20% require immediate insulin therapy since normal laboratory parameters where not achieved using oral sensitizers, sulfonylurea, diet and exercise; whereas those with $HOMA_{\beta cell}$ over 25% probably kept a functional pancreatic reserve capable of dealing with elevated glucose demands if combination therapy is started.

Patients that were incapable of responding to triple-combination therapy with oral agents have a different metabolic profile than those whom responded to treatment[34]. This probably reflects an irreversible β-cell failure represented in their $HOMA_{\beta cell}$ value (20%), showing that pancreatic β-cell is not able to normalize fasting nor post-pandrial plasmatic glucose levels but apparently is enough not to allow patients to fall into an extreme catabolic state (typical of a severe lack of insulin), which is commonly used as a clinical criteria to initiate insulin therapy, thus delaying the insulin therapy start[29]. Taken together all the above mentioned and using them from a clinical perspective, patients that fulfill this pattern should initiate insulin therapy before evident fat and proteic weight loss occurs (Table 1). $HOMA_{\beta cell}$ is able to distinguish β-cell functional capacity need to achieve glycemic control, at least during the follow up phase of this study. These patients are still being followed up in order to now if long term recovery of β-cell insulin secretory function can be achieved with triple combination therapy with oral agents with β-cell function of 25% or more.

$HOMA_{\beta\text{-cell}}$ determination in the clinical practice is a useful tool to assess when insulin therapy should be started type 2 diabetic patients. Moreover, it minimizes insulin misuse in patients that could still benefit from combination therapy with oral agents[13,26].

Initiation of insulin therapy in type 2 diabetic patients must be sustained on clinical knowledge and the analysis of the precise metabolic situation of each individual. The latter one can be supported through the interpretation of all laboratory parameters currently available for these means; and in this sense the information provided by a simple easy to apply mathematical method, such as $HOMA_{\beta cell}$, is very valuable[31]. It provides information of pancreatic reserve and the possibility of a better outcome in type 2 diabetic patients under conventional therapies. Furthermore, the estimated pancreatic secretory capacity guarantees an effective reduction in the deleterious use of insulin therapy in patients who can positively respond to oral agents and assure instauration of insulin therapy in those with minimal pancreatic insulin reserve, which influences in the life quality of our patients.

This mathematical model also allows us to quantify insulin–resistance levels by estimating $HOMA_{IR}$, which is a key element in the follow up of the natural evolution of the disease and the evaluation of different treatment approaches.

We considerer convenient to quantify insulin levels as well as to estimate $HOMA_{\beta cell}$ and $HOMA_{IR}$ in all type 2 diabetic patients not only in the means of diagnosis but also as a parameter to evaluate progression and therapeutic response in each patient. More studies that also support HOMA β-cell and HOMA-IR establishment as new criteria for initiating insulin therapy in type 2 diabetic patients are needed, so physicians can get more capable and comfortable with starting insulin programs.

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