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EDITORIAL

EASTER, THE RABBIT AND THE EGG: WHAT IS THE LINK BETWEEN THEM

The egg

The egg is a symbol previously of Christianity, that represents fertility and the rebirth of life. Many centuries before the birth of Christ, the trading of eggs was done in spring time, on the 21st of March, it was a custom that celebrated the end of winter and the beginning of spring. To obtain good harvest the farmers berried eggs in the field to cultivate. The Chinese used to have a tradition to cook eggs with beets that allows it to bring a characteristic color, and after they were dry, they were wrapped with onion peel and offered as a gift at the Spring Party. The Jews celebrated their escape from Egypt on Easter, for them the egg was a symbol of the people of Israel, once it doesn't lose its form after been cooked. Just like the Hebrews that were "cooked" for the suffering and the pain, but didn't lose their unity, identity and fidelity to Good.

After the death of Jesus Christ, the Christians consecrated this habit as a remembering of resurrection and in the 18th century, the church accepted officially the egg as a symbol of Easter. Its believed that the Church prohibit the Christians to eat eggs during the period of lent and those would celebrate the end of Holy week decorating eggs and distributing these colorful eggs to the kids.

The Orthodox of the East of Europe transformed the decoration of the eggs, that were usually painted with red, on a work of art. In Bulgaria, they have a custom to fight with eggs in their hands. The person who was able to conquer the challenge of maintain the egg intact up until the of the game was the most successful of the family until the next Easter.

Edward the 1st of England used to offered eggs dipped in gold to his preferred subjects. Luiz 14th of France distributed metal or porcelain eggs decorated and filled with a surprise to his friends. Luiz 15th presented his lover Madam du Barry with an enormous egg, with a statue of cupid inside. The eggs of Fabergé, inspired by the eggs of Easter, are master pieces of Jewry. They were designed by Peter Carl. Fabergé and his assistants worked for the czars of Russia during the period of 1885 to 1917.

Why chocolate?

In the 19th century, eggs begin to be filled with sugar and with some other fillings. Chocolate was available to Europeans only after the discovery of America when the Spanish met with the Aztecs, whom already had the habit of cultivating and processing cocoa.

In 1830, chocolate eggs started to be sold at the supermarket but we still don't know why and whom created chocolate Easter eggs but it is believe that it all started with the French.

The Rabbit

It is believed that the German's were responsible for introducing the rabbit into the Easter party. There are several explanations that try to justify the presence of this character in the Christian party. The well-known reproductive capacity of rabbits is associated with life, resurrection and to a new time of freedom, to the Jews as well as to the Christians.

The legend that only the rabbits saw Jesus' resurrection is also a well-accepted explanation. Others say that a very poor woman used to hide decorated chicken eggs in her backyard and challenged her children to find them. While they were playing this game, the kids saw a rabbit and started to tell people that it was the responsible for hiding the eggs. At the beginning of spring the rabbits were the first animals to abandon their holes which symbolized, many centuries ago, the rebirth.

On the other hand, in German mythology, the rabbit was the symbol of Ostara, the Goddess of fertility to whom the Spring party was celebrated. Even though, the Church wanted to ban pagan's cults, it included the image of the rabbit as a symbol of Christ's resurrection. In Brazil, brought by the Germans, rabbits, started to be a symbol of Easter at the end of 17th century.

Last but not least, Easter

Easter's origin is religious and it comes from the Latin word Pascae. In ancient

Greece, this term can also be found as Paska. Although, its most remote origin is related to the Hebrews, where the word Pesach was already used, and it meant passage. Greece was one of the first countries to celebrate Easter. The Greeks used to have this party on the first moon after the blossom of flowers, celebrating the fact that they were alive after the fiery winter of Europe. This date was also the same as the Hebrews exodus from Egypt on1250 b.c., where they were for many years, imprisoned by the Pharaohs. This story is told on the Bible's Old Testament, on the book of Exodus. Jewish Easter is also related to the Hebrews crossing of the Red Sea, where led by Moses they escaped from Egypt.

To Christians, Easter means resurrection of Jesus Christ. Nowadays, generally speaking, to the modern world, Easter means the sacrifice of Good's son and his ascendance to heaven, the rabbit means hope to a new life and the egg (even better if it is made of chocolate) means fertility and preservation of species.

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MINI REVIEW
DIABETIC NEPHROPATHY: ALWAYS A CHALLENGE

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Keywords: Chronic kidney disease, Diabetic nephropathy, Albuminuria, Glomerular filtration rate
Descritores :Doença renal crônica, Nefropatia diabética, Albuminúria, Taxa de filtração glomerular

Abstract

Diabetes Mellitus (DM) is observed in 50% of the cases of end-stage diabetic nephropathy (DN) and it is observed in patients with type 1 Diabetes and type 2 Diabetes. DN is the most common cause of end-stage renal failure in worldwide. DM is estimated to increase the risk of end-stage renal disease approximately 12-fold. Cardiovascular disease is the main cause of mortality in diabetic patients with DN. It is essential to have a proper screening and diagnosis of this disease to accomplish proper treatment and to delay its progression and mortality. **Endocrinol diabetes clin exp 2017 1959 -1961.**

Resumo

O diabetes *mellitus* (DM) está presente em 50% dos casos de doença renal crônica (DRC) terminal que ocorre pacientes com DM1 e DM2. A DRC de origem diabética é a causa mais comum de insuficiência renal em fase terminal em todo o mundo. Estima- se que o DM aumente o risco de doença renal terminal em aproximadamente 12 vezes. A doença cardiovascular é a principal causa de mortalidade em pacientes diabéticos com DRC. É essencial a triagem e o diagnóstico precoce desta complicação para seu tratamento adequado visando retardar sua progressão e mortalidade. **Endocrinol diabetes clin exp 2017 1959 -1961.**

INTRODUCTION

Diabetic Nephropathy (DN) is defined by specific structural and functional alterations. The most predominant structural alterations include mesangial expansion, glomerular basement membrane thickening, podocytes lesions and glomerular sclerosis associated with proteinuria (1,2). It is clinically observed through hypertension, edema, albuminuria, anaemia and hematuria (less frequent in patients with progressive chronic kidney disease), if diagnosed in early stage could delay the evolution to terminal disease (2,3,4).

DM is estimated to increase the risk of end-stage renal disease approximately 12-fold. Type 2 Diabetes Mellitus (T2 DM) accounts for 90% of diabetes and yet the natural history of nephropathy from prospective data is less well described for type 2 diabetes than for type 1 (5.) In type 1 diabetics the beginning of the disease is usually well known, an average, 15 to 20 years from the diagnosis. Also, data estimates that 20-30% of the patients will have a moderate increase of albuminuria after an average of 15 years from diagnosis but only half of those patients progress to an evident nephropathy. The progression of albuminuria is variable: the rates could increase, decrease or stay stable, depending on the factors related to glycemic control, blood pressure control and treatment with inhibitors of the angiotensin converting enzyme (ACE inhibitors) and angiotensin receptors blockers (ARBs) (2).

Diabetes is observed in 50% of the cases of end-stage of chronic kidney disease (CKD) and CKD is observed in 20-40% of the patients with type 1 diabetes and type 2 diabetes (6). Current data suggests that the risk of renal disease is equivalent for both types of diabetes. Evidences indicate that the time to develop proteinuria on early stages of diabetes and time of progression to end-stage renal disease are similar for both type 1 and type 2 diabetes. In type 1 as well as in type 2 diabetes some patients with moderately increased albuminuria, that obtain good control of diabetes, hypertension and dislipidemia could present a decrease of albuminuria (1,2).

THE USE OF ALBUMINURIA AND GLOMERULAR FILTRATION RATE FOR DN EARLY DETECTION

DN is the most common cause of end-stage renal failure worldwide. The incidence of clinical nephropathy in type 2 diabetes varies from around 5-10 % in Caucasians to 20-40% among certain other ethnic groups (7). Approximately one quarter of patients with type 2 diabetes, in a period of 10 years, develop microalbuminuria or a more severe nephropathy. It is estimated that half of patients who develop microalbuminuria do so within 19 years from diagnosis of diabetes. From any stage of nephropathy, the rate of deterioration to the next stage is 2-3% per year. Of patients who develop microalbuminuria, the average time to macroalbuminuria or severe renal disease is estimated to be 11 years. Hence, for patients diagnosed with type 2 diabetes later in life, the chance to have of significant renal impairment is low. In the contrast, for a person diagnosed earlier in life, the potential for renal failure increases (5). The inhibitors of the renin-angiotensin-aldosterone systems have their beneficial effect based on the preservation of glomerular filtration rate (GFR) as well as in the reduction of albuminuria. The use of ACE inhibitors or ARBs in diabetics with normal blood pressure and positive (>30mg/g) or moderate (30-300mg/g) albuminuria decreases the progression to more advanced stages of CKD. Approximately 40% of patients present spontaneous remission and do not progress to more advanced stages of the disease (6).

The need to a more efficient screening of DN and early disease intervention is well stablished. In diabetic patients, an early diagnosis of renal disease has been focused through the measurement of estimated albumin excretion rate (30-299 mg/24h) versus urinary albumin-creatinine ratio (30-299 mg/g) for the assessment of albuminuria to identify patients with increased risk of developing DN. When patients with type 1 diabetes develop evident nephropathy, the glomerular filtration rate (GFR) begins to decrease and it should be measured frequently to monitor the progression of the disease (8). Approximately 25% of patients with type 1 diabetes present with a decrease in GFR for normal rates of albuminuria, which denotes the importance of GFR calculation to diagnose, classify and evaluate treatment response. In the U.S., only 30% of patients with elevated urinary albumin-creatinine ratio progress to more advanced stages of CKD (8). The urinary albumin-creatinine ratio is susceptible to many interferences and in the case of abnormal test results, it must be confirmed using 2 or 3 samples with a 3 to 6 months interval. The American Diabetes Association(ADA) defines that an altered urinary albumin-creatinine ratio is greater or equal to 30mg/g (6).

Some of the more relevant data related to the development of CKD in diabetics were reported in the United Kingdom Prospective Diabetes Study (UKPDS) which was performed in a predominantly white population with type 2 diabetes. The UKPDS was designed to compare the efficiency of different types of treatment regimens with glycemic and blood pressu-

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re control as well as the related complications of diabetes in newly diagnosed patients (2). The study results showed that a decrease of 10 mmHg in systolic blood pressure was related to decreased number of diabetic microvascular complications, including diabetic renal disease (13%). Subjects that were recently diagnosed with type 2 diabetes and that received intensive treatment of diabetes and blood pressure showed a decrease of 30% of CKD incidence and progression and this protector effect perceived for 10 years. HbA1c <7% has independently reduced the risk of development and progression of CKD in type 2 diabetes (6). These findings demonstrated the importance of an early adequate blood pressure and glycemic control in DN primary prevention as well as in its secondary prevention (8).

The Diabetes Control and Complications Trial (DCCT, 1982-93) study on patients with type 1 diabetes, also showed that a HbA1c <7% was related with a decrease of 50% of development and progression of CKD. These positive effects were also persistent for 10 years of follow-up, according to Epidemiology of Diabetes Interventions and Complications (EDIC) (6,9).

The ADVANCE study, which included patients with type 2 diabetes, supports the relation between glycemic control and CKD, once its results found a decrease more than 50% in end-stage renal disease on its randomized group for intensive glycemic control, which persisted for 10 years (10). It was also observed that a decrease of a blood pressure of 140/73mmHg to 136/73mmHg (patients treated with perindopril-indapamide) decreased the risk for macro and microvascular complications as well as mortality (6).

The availability of a crescent number of drugs to treat type 2 diabetes supported the knowledge gap that still exist. Metformin is an important therapy that is under prescribed for patients with CKD, in some cases related to the risk of lactic acidosis. It is possible to use smaller doses (< 1g/day) in patients with stable renal insufficiency, with a plan to interrupt the use of this drug if significant intercurrence was observed. Although this strategy safety has been questioned, several guidelines (including ADA guidelines) suggest the use of metformin up to a GFR of 30ml/min/1,73 m2. When GFR is > 40ml/min half of dose will be used. Primary studies suggest that the agonist of GLP-1, dipeptil peptase-4 inhibitors (DPP-4) and sodium-glucose cotransporter inhibitor type 2 (SGL T2), mainly empagliflozin, promote renal protection, partially independent of its glycemic effects. The inhibitors of SGLT2 are of great interest, particularly because of its accentuated decrease of cardiovascular (CV) mortality and renal risk, as it was described on the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study (10). If GFR is ≤ 30 ml/min the studies are against the use of agonists of GLP-1. Linagliptina is the safer DPP4 inhibitor.

In patients with renal disease end stage, Lantus insulin should be indicated as it reduces the episodes of hypoglycemia.

Follow-up of patients with CKD, through HbA1c measurement is difficult for many reasons: first there is a reduction in blood cells mean lifetime at the end stage of disease, second when treating anaemia with erythropoietin or iron and finally because of hemoglobin alterations and mechanical destruction of red blood cells in dialitic patients. Some alternatives to HbA1c include frutosamine , glyicated albumin (except in nephrotic syndrome) and 1,5-anidrogucitol (except in terminal disease). The results of this ongoing studies are necessary to determine if these alternative methods are effective and if they are relevant in specific stages of CKD (10).

Another limitation of dueling with CKD is the increased risk of hypoglycemia. The increased risk of severe hypoglycemia in CKD portrays the mistaken use of some drugs like sulphonylureas and insulin, inadequate compensatory gluconeogenesis by the kidneys and presence of autonomic neuropathy. The most important components to treat those patients are glycemic control individualization, patient education, therapeutic planning, and hypoglycemia vigilance (10). The ACCORD study showed that in comparison with subjects with normal renal function, those that had creatinine of 1,3-1,5mg/dl presented an increase of 66% for severe hypoglycemia (6).

Cardiovascular disease is the main cause of mortality in diabetic patients with CKD (6). The increase of albuminuria may lead to increased cardiovascular disease directly, or may be a marker of an underlying abnormality such as enhanced platelet aggregability, accumulation in the endothelium of atherogenic lipoprotein particles or autonomic neuropathy. Patients with elevated plasma creatinine had a two to threefold increased rate of cardiovascular disease in comparison to subjects with macroalbuminuria only (5).

Traditional risk factors, including hypertension and dyslipidemia, are very relevant as well as the recent advances on intervention analysis which those are included as cardiovascular outcomes. Recent recommendations of Kidney Disease: Improving Global Outcomes (KDIGO) referent to the management of blood pressure and levels of lipids have set treatment strategies based on evidences that justify its incorporation in clinical practice. These strategies include blockage of RAAS with only one agent, ECA inhibitor or BRA and goals for a blood pressure below 130/80 mmHg in patients with diabetes and albuminuria. Treatment of dislipidemia in diabetic with CKD would be with low dose of statins of moderate intensity with or without ezetimbe (10). Statins would be prescribed in preference to fibrates. Patients with CKD have increased risk of myositis or rhabdomyolysis when statins and fibrates are used in combination (11)

…AND WHAT ABOUT DIABETIC KIDNEY ?

Glomerular hyperfiltration is a well characterized phenomenon in the initial phase of renal involvement in type 1 diabetes and has been regarded as a presumed risk factor in the pathogenesis of clinical nephropathy. Hyperfiltration is thought to be a maladaptive response to glomerular hemodynamics disturbances that eventually lead to development of CKD (7). In the initial stages of type 1 diabetes rates of glomerular filtrations increases around 30-40% specially in patients with poor metabolic control. There is a proportional increase of renal size, due to glomerular hypertrophy that is associated with progressive glomerular lesion development (6).

It is thought that hyperfiltration, at a glomerular level, is caused by increases in the glomerular capillary plasma flow rate and mean glomerular capillary hydraulic pressure, which in turn are due to changes in systemic blood pressure (SBP) and/or changes in efferent and afferent arteriolar resistance (7). There are hyperfiltration, even without hypertension, caused by vasodilatation of afferent and efferent arterioles in a lesser rate as shown by Hostetter and cols in 1981 (6). In type 1 diabetes, hyperfiltration carries a 53% risk of developing overt nephropathy compared with 5% in normofiltering subjects over a 17-year period. In type 2 diabetes, information on the prevalence and pathogenic significance of hyperfiltration is inconclusive and controversial, due to difficulties in defining hyperfiltration in this population; the co-existence of non-diabetic renal disease, the diversity of patient characteristics and the insidious onset of the disease (7). However, several current evidences suggest that in type 2 diabetes there is also the occurrence of hyperfiltration, but in a lesser rate when compared with type 1 diabetes (6).

The great majority of authors define hyperfiltration as a GFR greater than two standard deviations above the mean. The reported prevalence of hyperfiltration varies broadly from 6 to 75%, with high rates documented in new-onset diabetes. The filtration high rates may be explained, at least partly, by acute metabolic effect of hyperglycemia as well as by nephromegaly. Improved glycemic control has been shown to reduce GFR and kidney size. Long lasting hyperglycemia has also been correlated with increased GFR and in type 1 diabetes (1).

Hyperglycemia can be the only cause of an increased GFR, by a yet unknown mechanism. It is possible that there is a direct vasodilatation action over afferent arterioles, increasing plasmatic renal flux. There might also be indirect effects, an excess of glucose that may cause excessive proximal sodium reabsorption by cotransporters SGLT1 E SGL T2 decreasing ionport to the dense maculae, which leads to a signal that induces afferent arteriole vasodilatation and hyperfiltration. The mechanical stretching of the glomerular walls is one of the events capable of trigging a progressive process of glomerular lesions. The podocytes are the renal cells most sensitive to mechanical tension. Destruction of nephrons would lead to an even greater stress to the remaining units, perpetuating the process (6).

In non-diabetic individuals, the GFR "physiologically" decreases at a rate of approximately 1 ml/min/year after the age of 40-50 years. In a longitudinal study series of renal function in type 2 diabetic patients with a mean age of 62, the overall rate of decline of GFR was – 1.34 ml/min/year over 3.5 years and -1.2 ml/min/year over 5.5 years, with similar rates in normo- and microalbuminuric subjects, although considerable inter-individual variation was observed. The rate of GFR decline was signicantly correlated with a higher baseline systolic blood pressure, lower baseline GFR and higher albumin excretion rate and poorer glycemic control in the group not treated with anti-hypertensives. In current clinical practice, the discovery of microalbuminuria is considered to be the earliest predictor of clinical diabetic nephropathy (7) and chronic hyperglycemia it is its main risk factor (6).

Less than half of the diabetic patients develop severe renal lesions, possibly regarding the influence of genetic factors associated with this process (6,12). CKD has greater incidence rates in patients with positive family history for this disease and this risk is increased several times once one of their progenitors have hypertension, in those with extended duration of the disease or with other concomitant comorbidities (12).

Diabetic patients with persistent high blood pressure show a greater decline in renal function than normotensive patients. Dyslipidemia is also an important risk factor for CKD. Smoking habits are also another risk factor associated with CKD and quitting this habit has been associated with a decrease of the progression of renal disease (6).

CONCLUSION

The prevalence of diabetes is increasing worldwide in the last decades leading to a consequent increase of its complications, such as CKD. Early stage diabetic renal disease is usually asymptomatic and chronically progresses to a loss of renal function which will worsen patients quality of life and increases mortality by cardiovascular disease. Early diagnosis is difficult, although albuminuria and estimated glomerular filtration rate (GFR) are the best risk markers available in clinical practice for diabetic nephropathy they are not so important in early stages of the disease. In the early diabetes diagnosis glicemia, blood pressure and dislipidemia control are the most effective to avoid the development of DM chronic complications, Hence, it is essential that an early screening of CKD occurs to provide adequate treatment and to effectively delay its progression toward kidney failure.

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POINT OF VIEW
KIDNEY FUNCTION ESTIMATION IN PATIENTS WITH DIABETES MELLITUS: CKD-EPI VERSUS MDRD

AVALIAÇÃO DA FUNÇÃO RENAL EM PACIENTES COM DIABETES MELLITUS: CKD-EPI VERSUS MDRD

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Key words: Albuminuria, Glomerular filtration rate, Chronic Kidney Disease
Descritores: Albuminúria, Taxa de filtração glomerular, Doença renal crônica

Abstract

The incidence of diabetes mellitus (DM) has increased over the last two decades. In fact, DM is now the leading cause of end-stage kidney disease in most developed countries. Although albuminuria and estimated glomerular filtration rate (GFR) are the best risk markers currently available for diabetic kidney disease (DKD), they are less relevant in early stages of the disease. The most reliable method to estimate GFR in patients with DM is still a widely debated issue, since both equations, CKD-EPI and MDRD, underestimate GFR values in those patients. There are multiple barriers to arriving at a convenient equation to enable a timely diagnosis of DKD and optimizing the monitoring of patients in treatment. **Endocrinol diabetes clin exp 2017 1962 -1964.**

Resumo

A incidência de diabetes aumentou muito nas últimas duas décadas, a qual já é a principal causa de doença renal terminal na maioria dos países desenvolvidos. A albuminúria e a taxa de filtração glomerular (TFG) estimada são os melhores marcadores de risco atualmente disponíveis para doença renal do diabetes (DRD), porém, apresentam menor valor em estágios iniciais da doença. O melhor método para estimar a TFG em pacientes diabéticos ainda é largamente debatido, pois ambas as equações, CKD-EPI e MDRD, subestimam os valores de TFG em pacientes com DM. Existem várias limitações para se chegar a uma equação conveniente pela qual se pode diagnosticar de forma precoce a DRD, bem como otimizar o monitoramento de pacientes em tratamento. **Endocrinol diabetes clin exp 2017 1962 -1964.**

INTRODUCTION

The worldwide prevalence of diabetes mellitus (DM) has reached epidemic proportions. Incidence rates have increased dramatically over the last two decades, and it has been predicted that by 2040 there will be 642 million people afflicted by the disease (1,2). Diabetes is now the leading cause of end-stage kidney disease in most developed countries and the risk of this complication is estimated to increase by approximately 12-fold (2,3). Chronic kidney disease (CKD) occurs in 20-40% of patients with type 1 and type 2 diabetes (4). A substantial proportion of patients with a recent diagnosis of type 2 DM—around one-quarter of patients in 10 years—develop more severe microalbuminuria or nephropathy (3). To minimize those complications, CKD screening and timely interventions are required. Kidney disease is associated with a markedly high risk of cardiovascular disease and death in persons with diabetes (1,2).

The American Diabetes Association (ADA) and the Brazilian Diabetes Society (*Sociedade Brasileira de Diabetes*) recommended, in their 2016 guidelines, the use of the expression "diabetic kidney disease" (DKD) while the term "nephropathy" should be restricted to cases including proteinuria (4). The importance of estimating glomerular filtration rate (GFR) and measuring urinary albumin excretion is recognized for individuals with or without DM, as those two parameters are independent cardiovascular and renal outcome predictors and necessitate specific approaches. Given the relevance of GFR estimation in the evaluation, follow-up, and prevention of kidney disease, the differences and variability in the currently available methods will be discussed in the present paper (5).

MODIFICATION OF DIET IN RENAL DISEASE (MDRD) EQUATION OR CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In patients with DM, timely detection of DKD relies on urinary albumin excretion rate measurements. The presence of elevated rates indicating microalbuminuria (30-299 mg/24h or an albumin to creatinine ratio of 30-299 mg/g in untimed urine samples), identifies patients with increased risk of developing overt DKD with persistent macroalbuminuria (1). The ADA defines an abnormal albumin to creatinine ratio (ACR) for values of 30 mg/g or greater. The American Society of Nephrology and the KDIGO (Kidney Disease – Improving Global Outcomes) categorize ACRs into three ranges: normal (< 30 mg/g), increased (30-300 mg/g), and severely increased (> 300 mg/g) (4). Albuminuria and estimated GFR (eGFR) are the best risk indicators currently available for DKD; however, they are less valuable at early stages of the disease. The GFR in early-stage DKD is typically normal or increased and albuminuria frequently remits spontaneously. In addition, substantial structural damage is found preceding overt albuminuria, and for that reason the absence of albuminuria does not exclude DKD. In light of this, surrogate markers are needed to identify early-stage disease with greater precision (2). The most precise GFR assessment is attained through the clearance of inulin, a compound that fulfills the requirements of an optimal GFR marker, since it is totally filtered and is not reabsorbed, secreted, or metabolized by the renal tubules; however, it is an assay of difficult execution (4,6). Considering that direct GFR measurements are costly, GFR estimation is key to the diagnosis and evaluation of CKD, which is currently defined as an eGFR < 60 mL/min/1.73 m², persistently increased urinary albumin excretion (ACR > 30 mg/g creatinine), and abnormalities in imaging studies (4,7). The calculation of eGFR using empirical mathematical equations has been encouraged as a simple, fast, and feasible kidney function assessment method, and using a creatinine-based equation is the most common strategy for quantifying GFRs in clinical practice. However, this procedure could lead to an incorrect evaluation, especially in patients with normal kidney function, as in the early stages of DKD (6,8). A variety of equations have

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been proposed, such as Cockcroft and Gault's (1976), which was the most popular for many years given its simplicity. However, that equation is an estimate of creatinine clearance, not of GFR, and is particularly imprecise (7). The Cockroft-Gault equation typically overestimates the GFR and performs poorly in weight extremes, situations of catabolism, malnutrition, and amputated patients (4). In 1999, the Modification of Diet in Renal Disease (MDRD) equation was introduced. It was developed based on a study with 1628 patients, mostly white individuals (mean age, 51 ± 12.7 years) with non-DKD and a mean GFR of 40 mL/min/1.73 m², including only 6% of patients with diabetes (1,7,9). The equation included serum creatinine concentration and six other variables, later reduced to four: age, sex, race, and serum creatinine (7). Subsequently, the performance of the equation was extensively evaluated for other populations, including African-Americans, Europeans, and Asians with non--DKD, diabetic patients with and without renal disease, patients with liver disease, kidney transplant recipients, and potential kidney donors (9). Several limitations of the MDRD study equation have been reported, the major one being a systematic underestimation of GFR > 60 mL/min/1.73 m², which translates into overestimated CKD prevalence. The MDRD equation underestimates the mean filtration rate, and thereby tends to underestimate GFRs > 90 mL/min/1.73 m² (4,7).

The relationship between the GFR and serum creatinine levels differs for healthy individuals and patients with CKD. This physiological reality explains why the MDRD equation, developed from a population of CKD patients exclusively, underestimates high levels of GFR (7). This could also explain the limitations of the MDRD equation in predicting kidney function in healthy individuals and patients with early-stage DKD (1). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed in 2009 to enable a more accurate estimation of the GFR for individuals with normal or near-normal values (i.e., above 60 mL/min/1.73 m²). The CKD-EPI uses the same four variables as the MDRD equation, but the coefficients are different. The CKD-EPI equation was constructed using data gleaned from 10 studies of different populations comprising 8252 individuals. Of those, 73% had CKD and 29% had diabetes. The data were validated in comparisons with those obtained from 16 other studies in which the gold standard was direct GFR measurement using external filtration markers such as iothalamate. The study populations included individuals with and without kidney disease with a broad range of GFR levels (2,10,11). With a substantial proportion of individuals having a normal GFR, the overall performance of the CKD-EPI was superior to that of the MDRD equation (7). The CKD-EPI is more accurate, especially for GFRs within the normal range or slightly reduced (4). The improved performance of that equation is partly due to the inclusion of a diverse population in its design (2). The validation dataset for the CKD-EPI equation showed that it was as accurate as the MDRD study equation for individuals with eGFR < 60 mL/min/1.73 m² and somewhat more accurate for those with higher GFRs (10). Despite a marked reduction in bias when using the CKD-EPI equation, GFR estimates remain imprecise. Both the MDRD and CKD-EPI are based on serum creatinine and, as with all estimation equations relying on creatinine levels, they are subject to the same inevitable limitations of creatinine as a filtration marker. For patients with extremes of muscle mass, unusual diets, or conditions associated with decreased secretion/increased renal excretion of creatinine, all serum creatinine-based GFR estimates may lack precision(2).

The precision and bias of the CKD-EPI compared to those of the MDRD study equation may vary according to the GFR and various patient characteristics (11). The CKD-EPI equation has shown superior performance relative to the MDRD, with less bias and greater accuracy, but its precision is still limited—particularly across the normal GFR ranges (2). The CKD-EPI equation yields better results for higher GFR levels and in subgroups designated by sex, race, diabetes, and transplant status, for elderly individuals, and for patients with higher body mass indices (11).

The American Diabetes Association and the National Kidney Foundation recommend yearly urinary albumin excretion measurements and GFR estimation based on equations including serum creatinine, such as the MDRD and CKD-EPI. However, according to recent studies, those equations perform poorly with patients with DM and underestimate GFRs. Such disappointing outcomes seem to be related to the particularities of patients with DM, such as hyperglycemia, glomerular hyperfiltration, and obesity, which probably exacerbate the limitations of creatinine as a GFR marker. Hyperglycemia can interfere with equation performance in two ways. First, glucose levels > 300 mg/dL may impair the effectiveness of the Jaffe reaction in measuring creatinine concentrations. Second, creatinine levels may fail to reflect hyperglycemia-induced glomerular hyperfiltration, which is a typical phenomenon of diabetes (5). The most reliable method for GFR estimation in patients with DM is still widely debated. Rognant et al. compared the performance of creatinine-based formulas in a European population with diabetes. Results obtained with the Cockcroft-Gault, MDRD, and CKD-EPI equations were compared in 246 patients with GFRs measured using the inulin clearance method. In that population, the CKD-EPI was not superior to the simplified MDRD formula for GFR estimation. The CKD-EPI equation was shown to have a similar (or worse) performance to that of the simplified MDRD in that population of patients with DM as well as in specific subgroups defined according to the type of DM, GFR levels, or presence/absence of obesity. Various authors have reported superior performance of the CKD-EPI compared to the MDRD in the general population and in patients with DM; however, they were unable to corroborate the results obtained with the population of European patients with diabetes. This discrepancy could be due to differences between American and European patients with DM, including a greater proportion of black patients, a smaller number of patients with type 1 DM, and greater BMI in North America (8).

CONCLUSION

In addition to the problems associated with the reliance on serum creatinine values, the widely used estimation equations are less precise in some populations, including patients who have DM and high GFR. There are several barriers to obtaining a convenient equation through which a timely diagnosis of DKD could be established and the monitoring of patients already in treatment could be optimized (11,12,13). Both equations, the CKD-EPI and MDRD, underestimate the GFR of patients with diabetes. An ideal equation has not been designed so far. Nevertheless, the CKD-EPI seems to be the most appropriate equation to estimate GFR in patients with diabetes. Further studies are warranted to enable enhanced evaluations and advance the understanding of this topic.

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TOPICS IN MEDICAL CLINIC
ORIGINAL ARTICLE
SERUM VITAMIN D LEVELS AND SPONDYLOARTHRITIS ACTIVITY

NÍVEIS DE VITAMINA D E ATIVIDADE DE ESPONDILOARTRITES

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Key words: Spondyloarthritis, Inflammatory activity, Vitamin D.
Descritores: Espondiloartrite, Atividade inflamatória, Vitamina D.

Abstract

Background: Vitamin D (Vit.D) is known to favor an anti-inflammatory cytokine profile. **Aim:** To study if disease inflammatory activity in Spondyloarthritis (SpA) is associated with levels of serum vit. D. **Material and Methods:** We studied 92 SpA patients and 92 controls for serum levels of vit. D. SpA patients had epidemiological and clinical data collected from charts and disease activity measured by BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), ASDAS (Ankylosing Spondylitis disease Activity Score), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), hemoglobin (hb); MASES (Maastricht Ankylosing Spondylitis Score) of enthesitis activity and function through BASFI (Bath Ankylosing Spondylitis Functional Index). **Results:** Patients and controls had no difference in vit. D levels (p=0.36). In the Spa group, those with lower vit. D had higher BASDAI and lower Hb levels than patients with normal values (with p=0.01 and 0.04 respectively). No differences were found in the ASDAS MASES, ESR, CRP and BASFI (all with p=NS). **Conclusion:** Patients with low levels of vit.D had higher activity of SpA (measured by the BASDAI) than patients with normal values. **Endocrinol diabetes clin exp 2017 1965 -1967.**

Resumo

Justificativa: A Vitamina D (Vit.D) é conhecida por favorecer um perfil de citocinas anti-inflamatórias. **Objetivo:** Estudar se a atividade inflamatória da doença em Espondiloartrite (SpA) está associada com os níveis séricos de vit. D. **Métodos:** Foram estudados 92 pacientes com SpA e 92 controles para níveis séricos de vit. D. Nos pacientes com SpA foram coletados dados epidemiológicos e clínicos recolhidos a partir de prontuários e dados de atividade da doença medidos pelo BASDAI (Bath Ankylosing Spondylitis Disease Activity Score), ASDAS (Ankylosing Spondylitis disease Activity Score), velocidade de hemossedimentação (VHS), proteína C reativa (PCR); hemoglobina (hb); atividade inflamatória em enteses através do MASES (Maastricht Ankylosing Spondylitis Score) e função da através do BASFI (Bath Ankylosing Spondylitis Functional Index). **Resultados:** Pacientes e controles não apresentaram diferença em níveis séricos de vit. D (p = 0,36). No grupo Spa, aqueles com baixa vit. D apresentaram níveis mais elevados de BASDAI e de Hb menor que os pacientes com valores normais com p = 0,01 e 0,04, respectivamente. Não foram encontradas diferenças nas medidas do ASDAS MASES, ESR, CRP o e BASFI (todos com p = NS). **Conclusão:** Pacientes com níveis baixos de vit.D apresentaram maior atividade de SpA (medida pelo BASDAI) do que pacientes com valores normais. **Endocrinol diabetes clin exp 2017 1965 -1967.**

INTRODUCTION

Vitamin D (vit.D) has immune modulatory properties (1). This vitamin plays an inhibitory role in CD4, CD8 and B lymphocytes, dendritic cells and in the production of cytokines such as IFN γ, IL-2, IL-6, TNF-α. It is also known that vit.D increases the number of T regulatory cells and synthesis of other cytokines such as IL-4, IL-10 and TGF β (1,2). This profile suggests an action that down regulates immune responses. Epidemiologic studies demonstrated an association between vit.D deficiency and an incidence of autoimmune disorders such as systemic lupus erythematosus, diabetes mellitus and rheumatoid arthritis (RA) (2).

Spondyloarthritis (SpA) are chronic rheumatic diseases with Th1 and Th17 axis activation (3). They encompass a group of illness (Ankylosing Spondylitis, Psoriatic arthritis, Reactive arthritis and Arthritis associated with inflammatory bowel diseases) that affect mainly young males (4). The most distinguishing clinical feature is inflammation of axial joints (starting at sacroiliac joints) causing inflammatory low back pain. Eventually, the axial disease causes joint fusion, which is associated with substantial functional impairment and with the appearance of the classical “skier posture”. Patients may also present with asymmetric oligoarthritis (especially of the lower extremities), dactylitis (sausage digits), and enthesitis (inflammation at sites of ligamentous or tendon attachment to bone). Additional features include eye and bowel inflammation, an association with preceding or ongoing infectious disorders, and a strong association with the human leukocyte antigen (HLA)-B27 (4).

To correct manage SpA, the inflammatory activity must be controlled. Given the role of vit.D on immune functions, the level of this vitamin may impact SpA disease activity although studies in this area have contradicting results (5,6).

In the present study we aimed to know if Vit.D levels are associated with inflammatory activity in SpA patients from our region.

MATERIAL AND METHODS

After approval of local Committee of Ethics in Research and signed consent from participants, we studied 92 Spa patients and 92 healthy controls paired for gender and age from Curitiba - PR- Southern Brazil. This was a cross sectional study. All included patients fulfilled ASAS criteria (7) for SpA diagnosis and none had inflammatory bowel disease. We excluded patients using anticonvulsants, with creatinine ≥1.3 mg/dL, uncontrolled hypothyroidism and pregnant women. None of the included patients had vit.D replacement in the last year.

Serum 25 vit.D3 was measured by chemiluminescence by the Liaisom 25OH Vitamin D Assay (DiaSorin Inc., Stillwater, MN, USA). Values≥30 ng/dL were considered normal; between

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20-29 ng/dL as insufficiency and <20 ng/dL as deficiency.

Data on disease duration, epidemiological and clinical profile, HLA-B27 positivity was collected in medical records of AS patients. They had also determination of overall disease activity through BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) (8), ASDAS (Ankylosing Spondylitis disease Activity Score) (8), erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), hemoglobin (hb); enthesitis activity (through MASES or Maastricht Ankylosing Spondylitis Score (10); function through BASFI (Bath Ankylosing Spondylitis Functional Index) (8) and quality of life by ASqOL (Ankylosing Spondylitis quality of life questionnaire) measured simultaneously with vit.D.

Data was organized in contingency and frequency tables. Normality distribution was assessed by the Kolmogorov Smirnov test. Central tendency was expressed in mean and standard deviation (SD) in parametric samples and median and interquartile intervals (IIQ) in the non-parametric data. Association studies of nominal data were done through by Fisher Exact test and by Mann Whitney test, when data was numeric. The adopted significance was 5% (P≤0.05).

RESULTS

Controls had a median vit.D of 28.1 ng/dL (range 20.9-88.0 ng/dL) similar to those of SpA patients (median levels of 29.0; range 7.6-64.6 ng/dL); p=0.36. Table 1 shows the comparison between patients with normal and low vit.D3 levels. In this table is possible to observe that the disease activity measured by BASDAI was higher in those with lower levels of vit.D. Also, patients with low vit. D levels had lower level of median hb than those without it.

Table 1 - Comparison of epidemiological, clinical and disease activity data in spondyloarthritis (spa) patients (n=92) according to vitamin d levels.

Variable	Total (n=92)	Patients with vit.D <30 ng/dL N=48	Patients with vit.D ≥30 ng/dL N= 44	P
Gender (female/male)	35/57	21/27	14/30	0.23(**)
Age (years) Mean±SD	24-87 (48.1±11.7)	24-87 (49.6±13.1)	29-64 (46.5±9.7)	0.21(§§)
SpA forms	AS= 55/92 (59.7%) Apso=25/92 (27.1%) Others=12/92 (13.0%)	AS= 27/48 (56.2%) Apso=17/48 (35.4%) Others=4/48 (8.3%)	AS=28/44 (63.3%) Apso=8/44(18.1%) Others=8/44(18.1%)	0.49(**)
Uveitis	21/61 (34.4%)	7/30 (23.3%)	14/31 (45.1%)	0.07(**)
ESR (mm) Median (IQR)	1-120 20.0(10.0-44.7)	1-120 25 (10-49.5)	1-75 16.0(8.0-42.2)	0.22(§§)
CRP (mg/dL)	01-60,0 12,1(6,0-21,8)	0,1-60,0 11.0(5.0-21.1)	0,1-53,0 10.0(5.0-19.9)	0.77(§§)
Hemoglobin (g/dL)	8.1-18.0 14.3(13.0-15.1)	10.0-17.4 13.8 (12.9-14.9)	8.1-18.0 14.6 (13.2-15.7)	0.04(§§)
BASDAI	0-10 3.2±2.2	0-10 (3.8±2.3)	0-8.6 (2.6±1.0)	0.01(§)
MASES	0-14 0 (0-4)	0-14 0(0-3.2)	0-12 0.5(0-4.2)	0.94(§)
ASQoL	0-18 7.2±5.0	0-18 7.5(4.2-10.7)	0-17 7.0(2.2-12.7)	0.78(§§)
BASFI	0-9.1 4.1±2.6	0-9.1 4.5±2.7	0-9.1 3.7±2.6	0.26(§)

SD= Standard deviation; IQR= interquartile range; ESR= erythrocyte sedimentation rate; CRP= C reactive protein; BASDAI=Bath Ankylosing Spondylitis disease activity index; ASQoL= Ankylosing Spondylitis quality of life questionnaire; BASFI= Bath Ankylosing spondylitis functional index; MASES=Maastricht Ankylosing Spondylitis Enthesitis Score
P refers to comparison of patients with low and normal vit.D levels.
(*)-Fisher test; (**)-chi squared test; (§)- unpaired t test; (§§)- Man Whitney test

DISCUSSION

Our results showed that SpA patients and controls had same levels of vit.D. Previous studies have shown that patients may have lower, similar or even higher levels then controls (10). We also found a link between low levels of this vitamin and high disease activity measured by BASDAI. No associations could be found with ESR and CRP but it is well known that no serological marker is good enough to reflect the ongoing inflammation in SpA (11).

Durmus et al (5) and Langue et al (12) found association of SpA activity with low levels of vit.D but this could not be verified by Memerci-Baskan et al (6). This analysis may be complicated by variations of vit.D receptor and vit.D binding protein in the studied samples as it is well known that they suffer the effect of genetic background (10). Such variations may explain the dissimilarities found in the studies and highlight the need of local investigations.

Vit.D supplementation beneficial effects in SpA patients have not been proven. One study with psoriatic arthritis patients showed improvement in pain scores with administration of this vitamin. However, this was a very small study with only ten patients that had only one of SpA subtypes (10). More studies are needed in this context.

CONCLUSION

In the present study it was found that low levels of vit.D was linked to SpA high disease activity in patients from Southern Brazil. Further studies are needed to evaluate the value of vit.D reposition in this context.

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TOPICS IN MEDICAL CLINICAL
ORIGINAL ARTICLE
A SMALL STUDY ON DEPRESSION, GRIP STRENGTH AND BONE MINERAL DENSITY

UM PEQUENO ESTUDO EM DEPRESSÃO, FORÇA DA MÃO E DENSIDADE MINERAL ÓSSEA

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Key words: Depression, Muscle strength, Osteoporosis, Antidepressants
Descritores: Depressão, Osteoporose, Força muscular, Antidepressivos

Abstract

Background: Low bone mass is associated with several factors; recognizing them is useful for an early diagnosis of osteoporosis. **Objective:** To study possible associations of bone mass with depression and grip strength. **Material and Methods:** One hundred patients from a single rheumatologic center were studied for quality of life (by SF-12 instrument), independency in daily activities through Katz index, depression (by CES-D scale) and grip strength using a Jammar® dynamometer. Bone mass and epidemiological data were collected from patient's charts. **Results:** After correction for gender, age, ethnic background and smoking habits, it was found that the hip T score and hip density were negatively associated with depression (p=0.04 and 0.02 respectively). A trend towards association of spine bone density and grip strength was also found (p=0.07). **Conclusion:** Depression is associated with lower bone mass and its presence should alert the physician to act actively preventing and undertaking early diagnosis of osteoporosis. **Endocrinol diabetes clin exp 2017 1968 -1970.**

Resumo

Justificativa: Baixa massa óssea está associada com vários fatores que, se reconhecidos auxiliam no diagnóstico precoce da osteoporose. **Objetivo:** Estudar as possíveis associações entre massa óssea, depressão e força da mão.

Material e Métodos: Cem pacientes de um único centro de reumatologia foram estudados para qualidade de vida (pelo instrumento SF-12), independência nas atividades de vida diária através do índice de Katz, depressão (pela escala CES-D) e força da mão utilizando um dinamômetro Jammar®. Dados de massa óssea e dados epidemiológicos foram coletados por revisão de prontuários. **Resultados:** Após correção para gênero, idade, etnia e hábito de fumar, encontrou-se que o T score e a densidade mineral óssea do quadril estavam negativamente associados com depressão (p=0.04 e 0.02 respectivamente). Existia uma tendência para associação entre massa óssea da coluna com força da mão. **Conclusão:** Depressão está associada com baixa massa óssea e a sua presença deve alertar o médico para atuar energicamente na prevenção e no diagnóstico precoce de osteoporose. **Endocrinol diabetes clin exp 2017 1968 -1970.**

INTRODUCTION

Osteoporosis is a disease of growing impact as the world population becomes older. Looking for factors that highlight its presence is important for early diagnosis and treatment. Body mass index, gender, ethnic background and habits such as smoking, drinking alcohol and sedentary behavior, menopausal status and use of certain medications are some of the features that are taken into account when a physician decides to investigate this disease (1). Muscle strength and depression are also facets that should be accessed in this context.

Muscle strength and bone mass are closely linked (1), despite the fact that the specific relationships of muscle strength to bone mineral density (BMD) are poorly understood (2). There is a suggestion that the grip power in athletes and non-athletes is associated not only with local bone mass but also with bone mass at distant sites. However the studies in this area held controversial results (4-7). Age, gender, physical training, nutrition and humor disorders such as depression may interfere with muscle strength (8). Age-related decline in lean body mass with weakness is known as sarcopenia. There is a question if sarcopenia is a "normal" part of aging or a disease state. Despite this, it is well accepted that muscle mass could predict disability or mortality (8). Muscle mass is reduced in 15% each decade in the 6-7th decade of life and 30% in the following years (9). This may not only affect bone mass but also increase the risk of falls and fractures (9). The body composition also changes with age, with enlarged proportion of fat tissue. These changes are often followed by increased low-grade chronic inflammation and a deterioration in physical activity, a combination that favors osteoporosis (10).

Both muscle mass and muscle strength are inversely associated with depressive symptoms, mainly in the elderly (11). A study in a Chinese sample with 1046 individuals showed that those in the lower quartile of muscle strength had 3 to 10 times more chance of having depressive symptoms (11).

In the present study we aimed to evaluate the associations of bone mass with grip strength and depression as well as its influence in the quality of life.

MATERIAL AND METHODS

This is an observational cross sectional study that included 100 patients from a single Rheumatology center. The project was approved by the local Committee of Ethics in Research and all participants signed consent.

The patients were submitted to a measurement of grip strength, filled a questionnaire on depression (CES-D), SF-12 (for quality of life) and Katz questionnaire. Data on densitometry and epidemiological data were obtained through chart review. Densitometry should be done at least 6 months before data collection.

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The CES-D (Center For Epidemiologic Studies Depression Scale) is a screening test for depression in adults that has 20 questions on humor, behavior and perception and ranges from 0-60 (12). A score of 16 is used to identify minor depression and 27 for major depression. (13,14). The SF-12 (12-Item Short-Form Health Survey) considers only 12 items, with two domains: physical and mental health and it is a questionnaire that has been translated and validated for the Portuguese language (15). Grip strength was measured in triplicate, using a Jammar® dynamometer, in the dominant hand, with the patient in sitting position with elbow at 90o. For statistical purpose only the higher value was considered. The Katz index is a test in Independence in activities of daily living used to assess functional status as a measurement of the patient's ability to perform activities of daily living independently. Patients are scored yes/no for independence in six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment (16).

Obtained data was grouped in frequency and contingency tables. Association studies mass values with grip strength, depression, Katz index and SF12 were done with correction for age, gender and tobacco use through multiple regressions. The adopted significance was of 5%. Calculations were done with the software Medcalc 10.0.

Results

A - Description of studied sample:

The studied sample had 100 patients: 93% women and 7% man; 90% Eurodescendants, 6% Asians and 4% Afrodescendents; 38% were exposed to tobacco (12% present and 27% ex-smokers) and 61% were non-smokers. In this sample, 35% had diagnosis of osteoporosis according to OMS Criteria (16) and 36% had osteopenia. All studied women were post-menopausal.

Table 1 shows the results of studied variables in this sample.

Table 1 - Results of densitometry values, SF-12, Katz index, Grip strength and Depression scale in 100 individuals.

Variable	Range	Central distribution
Hip T score	-4.300 a +1.400	Mean -1.420±1024
Hip Z score	-2.300 a 2.100	Mean -0.147±0.947
Hip density g/cm^2	0.345-1.178	Mean 0.7697±0.1345
Spine T score	-4.700-1.100	Mean -1.910±1.170
Spine Z score	-2.900 a 3.400	Mean -0.336±1.342
Spine density g/cm^2	0.5180-1.160	Mean -0.8447±0.1311
SF-12 (physical domain)	15.7-57.90	Median -33.30 (IQR-24.04-43.18)
SF -12 (mental domain)	23.60-66.40	Median -52.70 (IQR-39.48-59-08)
Katz index	2.0-6.0	Median -6.0 (IQR-6.0-6.0)
CES D	1.0- 49.0	Median -15.0 (IQR-10.0-23.0)
Grip strength (mm Hg)	8.0-45.0	Median -20.0 (IQR- 18.25-25.0)

CES-D= Center For Epidemiologic Studies Depression Scale
SF-12=12-Item Short-Form Health Survey
IQR=interquartile rate

B - Studies of correlation of bone mass with functional studied variables

B1) Study of hip bone mass:

Studying hip T score by densitometry and correcting the values for age, gender, tobacco use and ethnic background through multiple regression no association was found with SF 12 physical domain (p=0.97) and mental domain (p=0.40), Katz index (p=0.16); hand grip (p=0.38) ;a positive association with depression was seen (p=0.04).

The same study using bone density measured in g/cm2 showed SF 12 physical domain (p= 0.4)) and mental domain (p=0.17), Katz index (p=0.14); hand grip (p=0.61) but, again, a positive association with depression (p-0.02).

B2) Study of spinal bone mass:

Studying spine T score by densitometry with correction for age, gender, tobacco use and ethnic background through multiple regression we found no correlation of SF 12 physical domain (p=0.87); SF12 mental domain (p=0.12), Katz index (p=0.68), hand grip (p=0.15) neither with depression (p=0.86).

When the study was done using bone density in g/cm2 it was found that there were no association with SF 12 physical domain (p= 0.98)) and mental domain (p=0.07), Katz index (p=0.77), depression (p-0.72), but a tendency towards hand grip (p=0. 07).

DISCUSSION

In the present study it was found that depression was associated with lower bone mass at the hip measured both by T score and bone density; grip strength only showed a trend towards an association with bone density in spine.

A case-control study that compared hospitalized depressed premenopausal young women to healthy volunteers demonstrated higher bone alkaline phosphatase and urine n-terminal telopeptide among the depressed women (18). Another study comparing the rate of hip fracture in people with and without depression in Taiwan, during a 10 year period, showed that patients with depression had 61% higher incidence of hip fracture than those without it (18). Hip fracture is an overwhelming disease with an acute mortality rate of about 5% and 1-year mortality rate of 15% to 25% (19). It has been found that 20%

of patients who suffer a hip fracture completely lose the ability to walk. It is possible that the connection between depression and low bone density varies with gender and/or race because some studies found a positive relationship for man (20), others for women (21) while others could not prove its existence (22).

There are some explanations to the link between depression and osteoporosis. First, depressed individuals may have apathy, negligence, motor retardation that results in low levels of physical activity, reduced sunlight exposure (resulting in deficiency of vitamin D) and poor nutrition that may contribute to decrease in bone mass (23). Secondly, they may also have increased cortisol levels and pro-inflammatory cytokines such as IL (interleukin)-1, IL-2, IL-6, TNF-α (22). And finally, the use of antidepressants probably contributes for its appearance. Among the modern antidepressants, the serotonin (5-HT) reuptake inhibitors (SSRI) are some of the most used. The discovery of functional 5 HT transporters in the bone has given rise to questions about the physiologic role of 5-HT in bone, and the subsequent clinical implications for humans (23). Williams et al. using data from the Geelong Osteoporosis Study to conduct an analysis of SSRI use and BMD found that SSRI use was associated with 5.6% lower BMD at the femoral neck with no differences were detected at the spine (24). Remarkably, we also found that depression associated with alterations in bone mineral density at the hip but not in the spine, but unluckily we had no data in the use of antidepressants. Other CNS active medications such as antidepressants, opioids, antipsychotics, anticonvulsants, and benzodiazepines increase the risk of falls and fractures mainly in the elderly (23).

We could not prove an association of grip strength with bone mineral density but a trend of association was found with spinal bone mass. Grip strength can be used as a surrogate for the whole muscle mass. Dixon et al found that in women low grip strength was associated with low bone mineral density at both the spine and hip and with an increased risk of vertebral fracture (25). It is possible that our sample was too small to demonstrate this association.

In the present study it was not possible to prove an association between bone mass with quality of life or independency for daily activities. This was an expected result as we did not study fractures but only bone mass.

This study has some limitations: it has a small sample and the values of bone densitometry were obtained retrospectively. However, it does highlight the association of depression with a lower bone mass and brings to discussion the need for vigorous actions for osteoporosis prevention in this group of patients.

CONCLUSION

Depression is a risk factor for low mineral density in the hip. Doctors who care for depressed patients should institute actions to prevent, to do an early diagnosis and treat osteoporosis.

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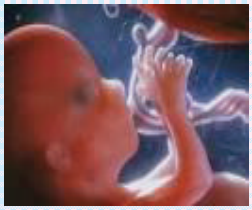
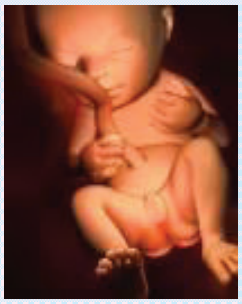
Congreso Latino Americano de Diabetes de la ALAD (11-2016).

Dislipidemia en lo embarazo

CONGRESO LATINO AMERICANO DE DIABETES DE LA ALAD (11-2016)




Dislipidemia en la gestaciòn

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Perlas sobre los resultados de la dislipidemia materna

Exposición del feto a la hipercolesterolemia y productos de su oxidación: Programación fetal de las células arteriais con predisposición a la aterosclerose en la vida adulta

- **No hay referencias para la normalidad del lipidograma durante el embarazo**
- **Aumento de peso , co-morbidades asociadas al Síndrome metabolico como la hipertrigliceridemia son factores de riesgo para morbi mortalidad de la madre y feto**
- **Diagnosticar y tratar la dislipidemia antes de la concepción reduce el riesgo de aterosclerose en la madre y hijo**

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Cardiol clín 2015; 33:209

Colesterol y desarrollo fetal

- Formación y integridad de membranas
- Sinalizacón de los recados de la transcripción gênica (hedgehog)
- Precursor de los esteróides sexuales y adrenais vitamina D y ácidos biliares
- Existencia de los receptores de LDL y receptores basureros SRB1) en la placenta y saco vitelino y células trofoblásticas
- Existe un activo transporte de las lipoproteínas placenta - feto
- Existe regulación de la entrada del colesterol para la circulación fetal por los receptores hepáticos LXR

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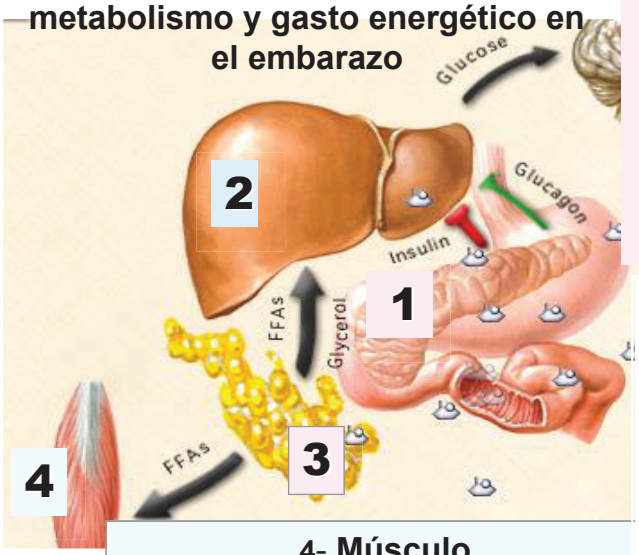
Órganos responsables por el metabolismo y gasto energético en el embarazo



1-Pancreas

Mayor demanda de la glucose

Mayor movilización de ácidos graxos

Hiperinsulinismo e Insulino resistência

2-Hígado

Acción del estrogênio aumenta la producción de triglicerídios(VLDL) y lipase lipoproteíca (LPL)

Aumento dela produción de glucose por el higado (S. metabólica)

4- Músculo

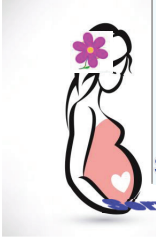
Almacena glucose para gasto energético

Sedentarismo

Aumento de la oferta de los ácidos graxos

3-Tejido gorduroso

Lipólise para el crecimiento y desarrollo fetal



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WILLIANS TEXTBOK 2006 MDCONSULT

La madre y lo metabolismo de las lipoproteínas

•Lo embarazo es uno estado fisiológico de la insulino resistência (hormônio placentário mamosomatotrófo)

•En las 6 primeras semanas de gestação hay una caída de lipídios circulantes

•En la 12ª semana aumenta el HDL que permanece elevado en todo lo embarazo

•Hay un aumento cada trimestre de lo colesterol total(CT), LDL y de los triglicerídios (TG)

•Aumento de lo colesterol hasta 250mg/dl es normal

Aumentos mayores 300mg/dl aumentam el riesgo de la mortalidade fetal

Cardiol clín 2015; 33:209

Hipertrigliceridemia

Eventos en la Madre

> 2000mg/dl riesgo de la pancreatite

•Síntomas neurológicos, neuropatia periférica,xantomas eruptivos,dolor abdominal (>500mg/dl)

•Pre eclampsia lo que llevaría a riesgo de albuminúria post gestacional - Enfermedad renal crónica

•Ganancia de peso

•Hiperurecemia

•Insulino Resistência – Diabetes gestacional

•Aumento de la permeabilidade vascular, alteraciones hemorreológicas

Cardiol clín 2015; 33:209

Exposición a la hipertrigliceridemia

Eventos em el feto

Alteración del tubo neural

El feto sólo tiene función pancreática después de la séptima semana

Cierre tubo neural - cuarta semana

- **Exceso de oferta de los ácidos graxos y glicose llevan la depleção embriônica del inositol que está conectado al cierre fisiológico del tubo neural**
- **Gran transferencia del colesterol y triglicerídios de la placenta para el feto**
- **Aumento del estresse oxidativo, ativação de las ceramidas y muerte celular**

Ind J Clin Bioch 2009;24:150

Exposición a la hipertrigliceridemia

Epigenética en la programación del desarrollo fetal

Eventos en el feto

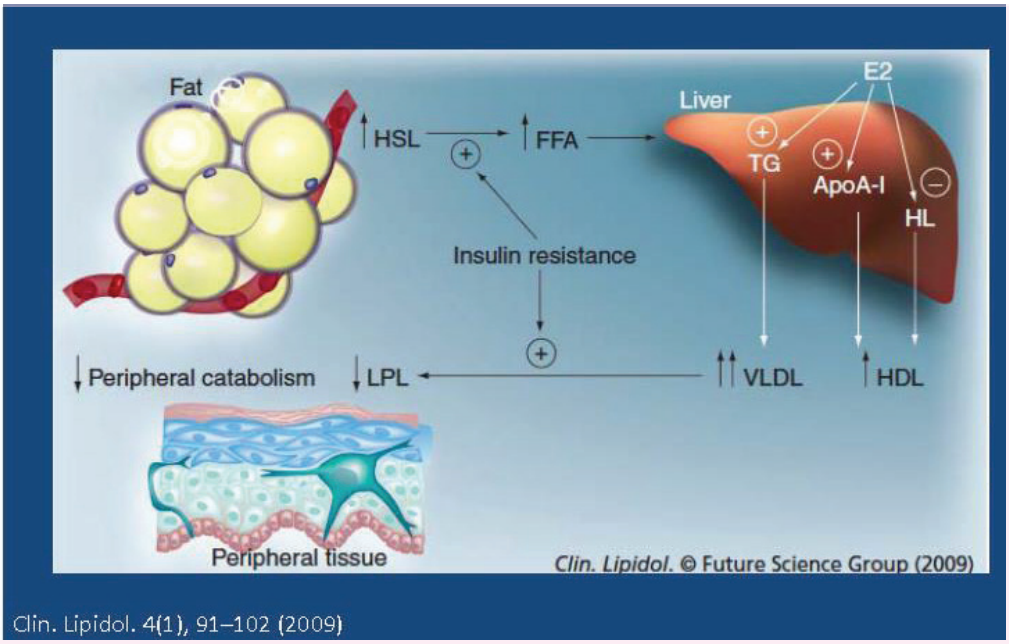
- **Metilação del DNA**
- **Acetilação de las histonas**
- **Alteraciones de los recados gênicos por micro RNA**
- **Modificación de la cromatina**
- **Up regulaciónde la síntese de los ácidos graxos**
- **Feto usa los lipídios para desarrollo y defensa de la membrana celular**
- **Exceso de grasa es depositada fígado dependiendo de la madurez hepática)**
- **Depósito de Grasa epicárdica**

Eventos de la protecion cerebral

Circ Res 2009;104:569

Hipercolesterolemia familiar

Principales cambios en el metabolismo de las lipoproteínas que ocurren en el embarazo avanzado



Clin. Lipidol. 4(1), 91–102 (2009)

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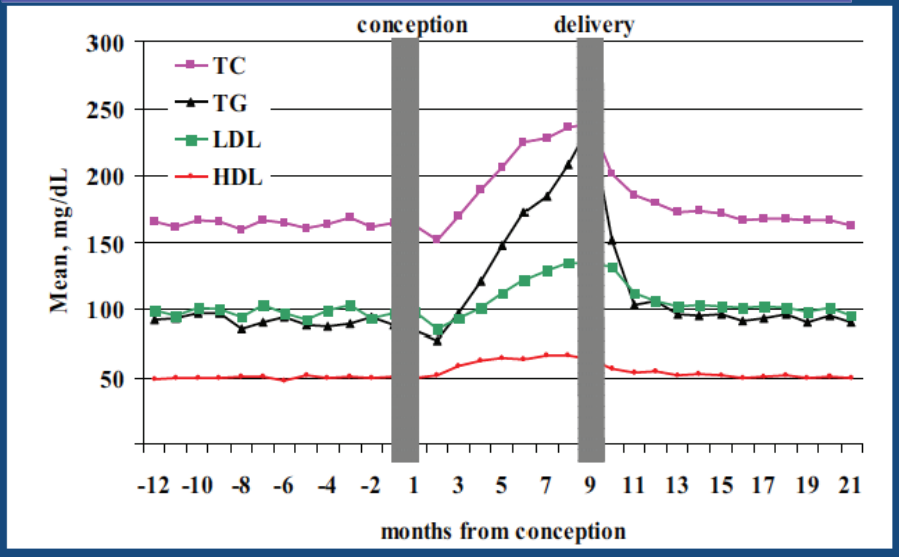
Niveles de los TC,TGs, LDL Y HDL : Durante Y 1 año post embarazo



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Lo que sabemos sobre la gravidez e hipercolesterolemia familiar

Recomendações de el estudo NICE Guidelines 2009

Planejar la concepcion com el colesterol lo más próximo possível de la normalidade

Retirarse la estatina 3 meses antes de la concepção

Mutação en el receptor de LDL – V408M aumenta la mortalidade fetal

Altos níveis de los estrogênios disminuem la PCSK9 (mecanismo de pós transcrição)

Cardiol clín 2015; 33:209

FELIC Study

Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study

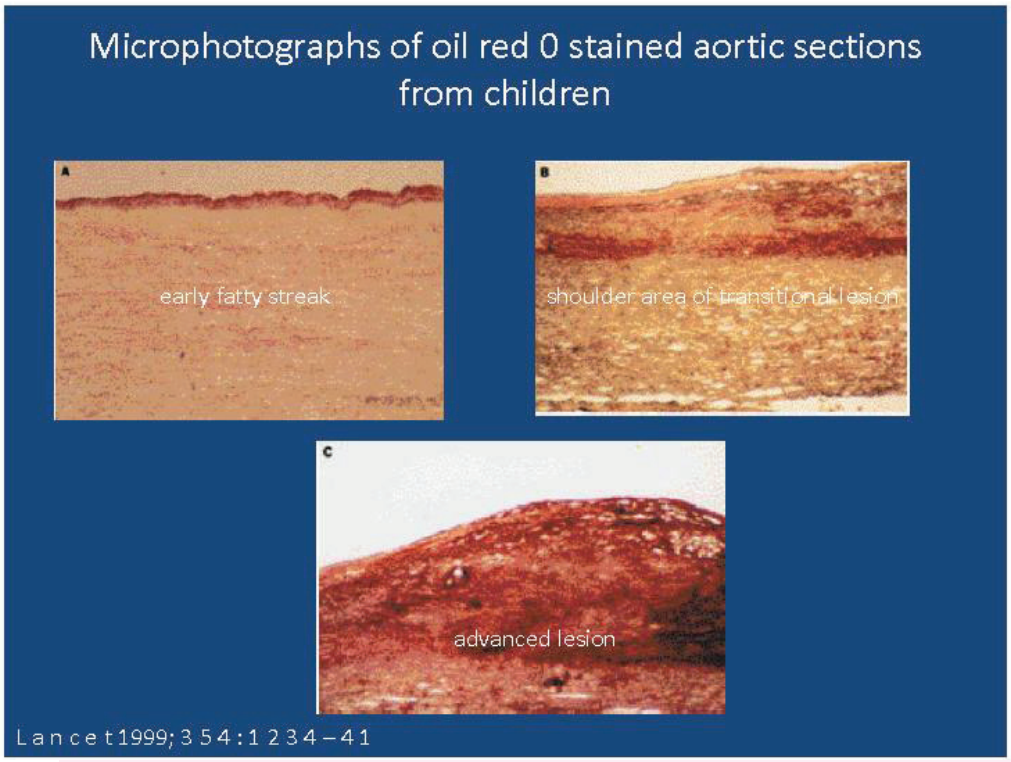
Claudio Napoli, Christopher K Glass, Joseph L Witztum, Reena Deutsch, Francesco P D'Armiento, Wulf Palinski

Our results suggest that maternal hypercholesterolaemia during pregnancy induces changes in the fetal aorta that determine the long-term susceptibility of children to fatty-streak formation and subsequent atherosclerosis.

If so, cholesterol-lowering interventions in hypercholesterolaemic mothers during pregnancy may decrease atherogenesis in children.

Lancet1999;354:1234–41

Cardiol clín 2015; 33:209



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Lipid Lowering Agents and Pregnancy Class

Lipid Lowering Agent	Pregnancy Class
Statins	X
Fibrates	C
Ezetimibe	C
Niacin	C
Cholestyramine	C
Colesevelam	B
Mipomersen	B
Omega3	B
Gemfibrosil	último trimestre B

Medscape visitado en abril 2016

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FH, Pregnancy & Apheresis

Low-Density Lipoprotein Apheresis Therapy During Pregnancy

Linda Cashin-Hemphill, MD, Margaret Noone, RN, Jodi F. Abbott, MD, Carol A. Waksmonski, MD, and Robert S. Lees, MD

"In conclusion, apheresis therapy with HELP was safe and efficacious during pregnancy in this patient with stable coronary artery disease and severe hypercholesterolemia."

The American Journal of Cardiology Vol. 86 November 15, 2000

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13 Mailing address of the main author must appear at the end of the article. Your article is your own responsibility, and the same answer for your account both within the medical ethics as in legal proceedings.

14 Structural definition of the main types of articles: Original articles: Articles Are produced through scientific research, presenting original data scientific findings with respect to experimental or observational aspects of Medical Biochemistry and social feature. Includes descriptive analysis and data inferences or own. In its structure should contain the following items: Introduction, Material and methods, results obtained and studied by an appropriate statistical method discussion and conclusion. Review articles: Are articles that seek to summarize, analyze, evaluate or synthesize research already published in scientific journals. The revisions are expected to be commissioned by the editors, except in case of scientific relevance for the medical class. Articles from Update or disclosure: These report updated information of interest to the magazine or a new technique or laboratory research. This topic is distinct in its account of the review article. Case report: Present descriptive data about a pathology with academic relevance in relation to the disease, treatment, laboratory or association with another pathology

15 The Journal of Endocrinology & Diabete clinical and Experimental use the peer review form of review the manuscripts Peer review is an important process for all authors to understand. Ultimately, peer review was created to protect scientific integrity and promote the sharing of research with other colleagues. It can help authors discover problems and helps to strengthen the credibility of their research. The extensive amount of published material relating to peer review can be overwhelming for readers to sort through, and this paper provides a relevant guide for authors regarding the peer-review process. The necessity of having quality control measures for published work is important to the scientific community, and without such measures, the quality of published work would not be what it is today. Peer review is necessary to identify scientific manuscripts worthy of publication and to improve the quality of published research


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