45 - CONJUGATED LINOLEIC ACID: IMPLICATION ABOUT THE CARDIOVASCULAR FUNCTION

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INTRODUCTION

The constant search for a better body image is a worry of the society today, seeking resources that enhance their efforts to achieve better physical shape. Among these features we find the so called thermogenic supplements that promise to facilitate the loss of body weight and measures through different ways. These have been gaining highlight due to the common lifestyle in our society, characterized by increased caloric intake and reduced physical activity, which, besides affecting the esthetic side, are connected to the appearance of several chronicle pathologic condition, such as obesity, diabetes, arterial hypertension and cardiovascular diseases (CVD). Given the interest, many specific nutrients have been researched, especially fatty acids, with capacity of interfering on the lipids metabolism of the organism, being able to act as support in the treatment or prevention of obesity and of its comorbidities.

The conjugated linoleic acid (CLA) is a term used to refer to a set of positional and geometric isomers of the octadecadienoic acid. It is produced naturally by the biohydrogenation and isomeration of fatty acids by bacteria present in rumen of different animals, such as cows and goats. The main natural source of CLA is the meat and dairy products coming from these animals. Among the different isomers existing, the most biologically active are the cis-9, trans-11 and trans-10, cis-12, being the first the predominant form found naturally in the food, and the second most common in handled products, like supplements, which are generally composed of a mix of isomers, with approximate 50:50 of each isomer, plus a minimum quantity of other less common isomers (Bhattacharya et al., 2006). The existence of several isomers explains the several biological activities performed by the compound. Until now, the following benefic effects are attributed to CLA: body weight reduction, with reduction of the body fat and continuity/increase of the lean body mass; improvement of the insulin sensibility; anticarcinogenic and cardiovascular protective action (BHATTACHARYA et al., 2006; NAGAO et al., 2003a; NAVARRO et al., 2007; PARK & PARIZA, 2007).

Due to the pursuit and dissemination of the product, especially as facilitator of weight loss, the use of CLA has been very widespread. However, futher studies are needed about the safety of its use, especially if supplemented for long periods of time, given the possible negative effects of the use of CLA over the resistance to insulin and emergence of hepatic steatosis (KENEDY, et al., 2010). Thus, the review aims to provide an overview of studies with the conjugated linoleic acid and its effects on the cardiovascular function, system directly related to the process of changes of the body composition.

The CLA in the reduction of the fat and body weight

The relationship between obesity and CVD is already well established; however the ways which this connection happens is not well explained. Despite of what was thought, today it is known that the adipose tissue isn't only an energy stored tissue; but an endocrine tissue with active production involved in the control of the body homeostasis, with neuro endocrine and immune function. Among the wide variety of compounds produced by the adipose tissue, there are the adiponectin, leptin, angiotensin, TNF-α and interleucine-6 (IL-6). The alteration suffered by the adipocites in the process of installation of the obesity has consequences in the secretion of the adipocines mentioned, that are related with the pathologic implications of the obesity, as the cardiovascular risk (ATHYROS et a., 2010, JO et al,. 2009, MATSUZAWA, 2005)

Since the observation of its reducer activity of the body fat, has been proposed that the trans-10, cis-12 is the principal isomer involved (PARK ET AL., 1999). The reduction of the body fat mediated by the CLA happens through different ways, like the increase of the energetic spent, reduction of the fat capitation by the adipocites, reduction of the differentiation of pre-adipocites, and increase of fatty acids β-oxidation. The increased energy expenditure happens by the increase in consumption of oxygen (PARK; PARIZA, 2007) or by the increase of the expression of the uncoupling proteins (UCPs), deviating the energy of the production of adenosine triphosfate (ATP), that if not used is rapidly stored, dissipating this energy as heat (KENNEDY et al,. 2010; PARK; PARIZA, 2007).

In addition, the supplementation with CLA has been associated with the decreased expression of the neuropeptide Y in the hypothalamus, hormone that leads to an increased foods intake, reinforcing the hypothesis that this fatty acid acts in the genes of regulation of the appetite (CAO et al,. 2007). So, Tse e Li (2009) observed that rats supplemented with the isomer trans-10, cis-12 had an approximately 24% redution of food intak, accompanied by a reduction in the expression of the neuropeptide Y. The reduction of the feed intake was also observed by Hernandez-Diáz (2010). On the other hand, Declerq; Zahradka and Taykor, (2010) and Park et al. (2010) did not check this reduction.

The CLA has inhibition effect of the peroxisome proliferator-activated receptor (PPARs), more specifically the PPARγ, that belongs to the super family of the nuclear receptors and acts as transcription factors, regulating the expression of several genes (target genes). Among the target genes of the PPARγ are several regulator genes of the lipid metabolism and adipogenesis process (KENEDY et al., 2010; KANG et al., 2003). The PPARγ is involved in the initial stages of the differentiation of the preadipocytes in adipocytes, as observed by Kang et al. (2003), that checked that supplementation of CLA, particularly the trans-10, cis-12, was accompanied by reduction in the expression and activity of the PPARγ, followed by a slower rate of differentiation of preadipocytes in adipocytes and increasing the rate of apoptosis of these cells. The suppression of the PPARγ also inhibits the lipogenesis, being the biggest activator of lipogenic genes. It had been observed the reduction of enzymes like lipase lipoprotein (LPL), stearoyl-CoA desaturase (SCD), Acetyl CoA descarboxilase (ACC) and fatty acid sintase (FAS) due to the supplementation of the CLA (PARRA; SERRA; PALOU 2010; LA ROSA et al., 2006; BROWN et al., 2003). Inhibition of SCD may explain the higher concentrations of saturated fatty acids with lower monounsaturated during CLA supplementation.

Added to the inhibition effect o the lipids accumulation, La Rosa et al. (2006) observed the stimulation of expression of sensitive hormone lipase (SHL) in the white adipose tissue, Increasing the β-oxidation of the lipids with the administration of the CLA in human adipocites just-differentiated. Furthermore, this increase seems not to prolong, reducing with the continuous use of the CLA. The second way which CLA stimulates the lipolysis is related to the bigger concentration of proinflammatory factors due

to the inhibition of the action of the PPARy (KENEDY et al,. 2010; PARK; PARIZA, 2007). Finally the CLA promotes a higher expression of CTP in the cells of several tissues causing the capitation and use of fatty acids by the mitochondria (KENEDY ET AL,. 2010).

The CLA and lipid profile

Several are the risk factors for the cardiovascular diseases, being the profile of serum lipids one that deserves to be spotted. The elevation of serum LDL with the reduction of HDL can result in fat accumulation on vassel walls, featuring the atherogenic process. The CLA has shown effects on total cholesterol and fractions and serum triglycerides in different animal models or humans studies, being the results of the studies not consistent about the effect or daily dose, thus depending of the draw of the design of the study to the supplementation with CLA did not have meaningful effects about HDL, LDL, VLDL (COOPER et al., 2008; BROWN, TRENKLE e BEITZ, 2010; RAFF et al., 2008) and can increase TG (COOPER et al,. 2008). Many others show the effect of improvement of aspects of the lipid profile, with reduction of the serum TG, which is considered as a independent risk factor for CVD (HERNANDÉZ-DIÁZ et al., 2010, HUR et al, 2005), besides the improvement in the total cholesterol and HDL (KENEDY, 2010, NESTEL; FUJII; ALLEN, 2006).

Data revised by Bhattacharya et al. (2006), show experimental rehearses with animals in which the CLA seems to be more efficient when there is a dietetic factor of risk for CVD, like diets with excess of simple carbohydrates, lipids and / or rich in saturated fatty acids, or obesity. Diniz et al. (2008), in a work with rats, checked that the group which obesity was induced by the sucrose, the CLA had meaningful effect, with reduction of total cholesterol, HDL, LDL and of the reason HDL/TG. Therefore effects in humans, especially on the health ones, keeps controversial (KENEDY et al,. 2010, GAULIER, 2004)

One of the hypothesis for the effect of the CLA on the serum lipids is its action on the PPARγ and SREPB-1c (sterol regulatory element-binding proteins), both involved with the lipids metabolism (KENEDY ET al., 2010). The CLA presents effect about the expression of SREPB-1c in the liver, being the isomer cis-9, trans-11 related to this effect while the trans-10, cis-12 did not have such capacity. The SREPB-1c is associated to the synthesis of fatty acids, regulating enzymes like FAS and ACD (ROCHE et al,. 2003). Such difference can explain the observations of Arbonés-Mainar et al. (2006), verifying that, in rats ApoE_/_, the isomer cis9,trans11 reduces the serum cholesterol and the non essential fatty acids (NEFA) and increased apo AI, while the trans10,cis12 increased the total cholesterol, NEFA, HDL, TG and apo B, besides resulting a condition of hyperglycemia in the animals.

CLA and atherosclerosis

Most of the cardiovascular events are involved with the development of the atherogenic plaque. The researches with CLA and atherosclerosis, until now, are contradictory, being the comparison between its results made harder by great differences that happen in the doses and isomers prescribed, and in the design of the treatment. The CLA can act inhibiting the process of formation of fat streaks and atherogenic plaques or lead to resolution of these lesions depending on the level of commitment. Other studies, however, do not find effects of none of the two isomers about the formation of the plaques or about the ones already formed (COOPER ET AL., 2008, NESTEL; FUJII; ALLEN, 2006). Arbonés-Mainar et al. (2006) related the difference of action between the two main isomers of the CLA. Rats ApoE were fed with isocaloric diets with 0,15% of cholesterol and 1% of cis-9,trans-11 or trans-10,cis-12 or linoleic acid, being observed that the isomer trans-10, cis-12 presented a pro-atherogenic effect, with higher atherogenic lesions and less stable plaques, while the isomer cis-9, trans-11 had opposite effect, protecting the aorta against the atherogenic lesion.

One way by which the CLA can interfere in the atherogenic process is through the regulation of the PPARs, important gene modulators, especially of genes involved in the lipid metabolism. (TOOMEY, 2005; YU ET AL,. 2002). A key point of the atherogenesis is the formation of foamy cells from the macrophages, which is related with the rates of influxes and efflux of the macrophage cholesterol. The PPARs are important modulators of this homeostasis of the cholesterol in the macrophages (BARBIER et al., 2002; DURVAL et al., 2002). Some studies with pharmacological ligands of PPARs show the capacity of reducing one of the mechanisms of capitation of LDL cholesterol modified, and inducing to the gene expression ABCA1, which promotes the eflux of the cholesterol of the macrophage, constituting thus a possible therapy antiatherogenic (CHINETTI et al, 2001; CHAWLA et al,. 2001). However, evaluating human macrofagos in vitro treated with CLA, that is considered a ligand for PPARy and PPAR α, did not find promising results like the pharmacologic ligands (WELDON et al,. 2004).

CLA can inhibit or resolve atherosclerotic plaques by the capacity of reducing the oxidation of the LDL, which leads to the stabilization of the plaques. CLA stimulates the synthesis of glutathione without peroxidation lipid, inhibits the expression of mRNA for cyclooxygenases 2 (COX2) and induces the synthesis of nitric oxide, protecting against the oxidative stress. Besides this, studies relating CLA and cancer showed that this fatty acid can increase the activity of the antioxidant enzymes, like superoxide dismutase (SOD), catalase and glutathione peroxide (Yang et al,. 2000, BHATTACHARYA et al., 2006). Finally the CLA modulates the synthesis of reacting oxygen species (ROS) and the activity of the cytoplasmic phosphatase A2, involved with the anti-inflammatory effect attributed to CLA (DUBICK; OMAYE, 2001, NAKAMURA et al, 2009).

CLA and hypertension

Hypertension is a common risk factor for CVD and its control must be involved on the prevention or treatment of the same. Researchers using animal models (INOUE et al., 2004, HENANDÉZ-DIAZ et al., 2010, NAGAO et al., 2004), and humans (IWATA et al.,2007) tested the efficiency of the CLA on the blood pressure, and several of them had positive results. With humans was observed the benefic effect of the CLA on the values of blood pressure of pregnant women who developed pre-eclampsia (HERRERA et al., 2005) and its potentiated effect of hypotensive drugs in hypertensive Chinese patients dependent of medication was observed (ZHAO et al., 2009).

Henandéz-Díaz et al. (2010) using SHR rats found a smaller increase of the blood pressure in the group in which the CLA was used. Inoue et al. (2004) also working with SHR young to evaluate the effect of the supplementation of CLA during the process of development of the hypertension, it was observed that the systolic pressure of the group that received the CLA had lower elevation and an increase of the mRNA of adiponectin, involved in the control of the blood pressure. On the other hand, PARK et al. (2010) did not have similar results, even using SHR rats. Such discordance can happen due to the difference in the quantity of CLA offered or in it composition. Still without a reduction of the pressure, there was a meaningful reduction on the incidence of heart attacks or symptoms similar to the infarct in the group that received CLA.

It is known that the adipose tissue has a local system of renin-angiotensin, that can affect the levels of serum angiotensinogen and the blood pressure, and interfere in the production of pro-inflammatory citocin involved in the pathogenesis of the cardiovascular disease, being able to constitute a pathway which the CLA acts on the blood pressure (DECLERQ et al., 2010, MASSIERA et al, 2001, KOUYAMA et al., 2005, SANZ-ROSA, 2005, RODRIGUEZ-ITURBE et al., 2005). Another possible

mechanism is by the modulation of the adiponectine by the adipose tissue. This adipocin is related with the activity of the nitric oxide endothelial sintase, which produces an important vasodilator (NAKAMURA, 2009). A protector effect of the adiponectin over the atherosclerosis has been shown. The serum levels of adiponectin is inversely proportional to the mass of the adipose tissue, thus the complications of the obesity might be due to the dysfunction of the adipocite, seen that the adiponective has been seen as a good marker for the function of this cell (TRUJILLO; SCHERER, 2005).

CONCLUSION

In the face of the data revised, although there is a certain disagreement among the studies, it seems that there is a protector effect and improvement of the cardiovascular function by CLA. The pathways throughout this effect occurs remain to be clarified, but it is known that this fatty acid has influence on the lipid metabolism and on the adipose tissue, affecting its dimension and secretions, fact that has connection with regulation of the blood pressure, lipid profile and other risk factors for CVD. Although, these studies are predominantly in animal model and in vitro; the trials with humans are inconclusive and need futher evaluated to ensure the correct and safe use of the conjugate linoleic acid as nutritional supplement.

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CONJUGATED LINOLEIC ACID: IMPLICATION ABOUT THE CARDIOVASCULAR FUNCTION

ABSTRACT

The conjugated linoleic acid (CLA) refers to a set of isomers of the octadecadienoic produced naturally by bacteria present in the rumen of the animals, which has been used as alimentary supplement, as it potential body fat reduction effect. Several biological activities are attributed to the compound, such as cardiovascular protector, although the mechanisms which CLA interferes in this function are still not established. Primarily, the CLA acts on the serum lipid profile being able to alter the levels of total cholesterol, LDL, VLDL, HDL and TG, important risk factors for the CVD, such action is probably due to the capacity of regulating the synthesis of lipids, being associated also to reducing acting of fat and consequently, the body weight. The CLA also appears to have effect on the atherogenic process, observing positive effects over the atherosclerotic places established and in the process of deposition of lipids in the vessels, besides establishing for formatted places. Finally, towards the arterial pressure, the CLA seems to have the capacity of reducing blood pressure. However, the results found are not consistent yet, specially, in models with humans, thus, future studies must be done to determine a daily recommended dose and the safety of its use.

KEY WORDS: CLA, CARDIOVARCULAR, LIPIDS

L'ACIDE LINOLÉIQUE CONJUGUÉ: INCIDENCE SUR LA FONCTION CARDIO-VASCULAIRE

RÉSUMÉ

Lacidelinoléique conjugué (ALC) est un ensemble d'isomères de l'acide octadécadienoique produite naturellement par les bactéries présent dans le rumen d'animaux, et ces't utilisé comme supplément alimentaire, à cause de son effet potentiel réducteur de la graisse corporelle. Plusieurs activités biologiques sont attribuées à cet composé, par exemple, la protection cardio-vasculaire, malgré les mécanismes par lesquels l'ALC intervient dans cette fonction sont pas toujours bien établis. Premièrement, l'ALC agit au profil lipidique sérique et Il peux modifier les niveaux de cholestérol total, LDL, VLDL, HDL et TG, qui sont importants facteurs de risque pour le maladie cardio-vasculaire. Cette action est liée, probablement, à la capacité de réglementer la synthèse des lipides, et aussi associé à l'action réductrice de la graisse et, en conséquence, du poids corporel. L'ALC peut possiblement interférer aussi au processus d'atherogenie, avec dês effets positifs sur les plaques de l'athérosclérose

établies et dans le processus de dépôt de lipides dans les vases, et aussi stabiliser des plaques formées. Finalement, concernant la tension artérielle, l'ALC a possiblement la capacité de réduire la tension sanguine. Néanmoins, les résultats trouvés ne sont pás toujours cohérents, spécialement, dans les modèles avec des humains. De cette forme, des études futures doivent être réalisées pour déterminer la dose quotidienne recommandée et la sécurité de cette utilisation.

MOTS CLÉS: ALC, cardio-vasculaires, lipides

ÁCIDO LINOLEICO CONJUGADO: IMPLICACIONES SOBRE LA FUNCIÓN CARDIOVASCULAR

RESUMEN

El ácido linoleico conjugado (CLA) se refiere a una serie de isómeros del ácido octadecadienoico producida naturalmente por bacterias presentes en el rumen de los animales, que se ha utilizado como un suplemento alimenticio debido a su efecto potencial en la reducción de grasa corporal. Diversas actividades biológicas son atribuidas al compuesto, como el caridiovascular guardia, y los mecanismos por los cuales CLA afectan a esta función todavía no está bien establecida. En primer lugar, los actos de CLA en el perfil de lípidos pueden alterar los niveles de colesterol total, LDL, VLDL, HDL y TG factores, el riesgo significativo de enfermedad cardiovascular, tal acción se debe, probablemente, la capacidad de regular la síntesis de lípidos, acción también se asocia la reducción del peso de grasa corporal y por lo tanto. El CLA también parece tener un efecto sobre el proceso aterogénico, la observación de efectos positivos en establecer las placas de ateroma y en el proceso de deposición de lípidos en los vasos sanguíneos y estabilizar las placas formadas. Por último, en relación con la presión arterial, el CLA se parece tener la capacidad de reducir la presión arterial. Sin embargo, los resultados siguen siendo inconsistentes, especialmente en los modelos con los seres humanos, por lo tanto, futuros estudios deben llevarse a cabo para determinar la dosis diaria recomendada y la seguridad de su uso.

PALABRAS CLAVE: CLA, cardiovascular, lípidos

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RESUMO

O ácido linoléico conjugado (CLA) refere-se a um conjunto de isômeros do ácido octadecadienoico produzido naturalmente por bactérias presente no rúmen de animais, que vem sendo usado como suplemento alimentar, visto seu potencial efeito redutor da gordura corporal. Várias atividades biológicas são atribuídas ao composto, como a de protetor cardiovascular, sendo que os mecanismos pelo qual o CLA interfere nessa função ainda não bem estabelecidos. Primeiramente, o CLA atua sobre o perfil lipídico sérico podendo alterar os níveis de colesterol total, LDL, VLDL, HDL e TG, importantes fatores de risco para as DCV, tal ação é decorrente, provavelmente, da capacidade de regular a síntese dos lipídios, sendo associado também ação redutora da gordura e, consequentemente, do peso corporal. O CLA também parece ter efeito no processo aterogênico, observando-se efeitos positivos sobre placas ateroscleróticas estabelecidas e no processo de deposição de lipídeos nos vasos, além de estabilizar placas formadas. Por fim, em relação à pressão arterial, o CLA parece ter a capacidade de reduzir a pressão sanguínea. Entretanto, os resultados encontrados ainda não são consistentes, especialmente, em modelos com humanos, desta forma, estudos futuros devem ser realizados para determinar dose diária recomendada e a segurança do seu uso.

PALAVRAS-CHAVE: CLA; cardiovascular; lipídeos.