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## **Atherosclerotic lesion formation in rabbits fed on egg yolk-supplemented diet: an inexpensive experimental model**

*Formação de lesão aterosclerótica em coelhos alimentados com dieta suplementada com gema de ovo: modelo experimental de baixo custo*

The paper "Atherosclerotic lesion formation in rabbits fed on egg yolk-supplemented diet: an inexpensive experimental model" published in this journal in December 2006 was directed at finding an animal model that presented similar characteristics to human atherosclerosis. Several efforts have been made to find this ideal model, and all studied species have both strengths and limitations. In the aforementioned paper, atherosclerosis was induced by feeding rabbits with egg yolk for 90 days. Although its cost is lower than other methods described in the paper, the atherosclerotic lesions obtained with egg supplementation were quite modest. It was not clear if there were significant differences in lipid profile between the control and treated groups. However, even if significant increases in plasma lipids were observed in the animals submitted to the egg diet, histological findings were not robust.

Mild atherosclerotic lesions might have been due to the effects of egg yolk in lipid metabolism. There are a number of studies demonstrating that egg yolk is able to promote an increase in either plasma HDL-cholesterol (HDL-c) and in LDL-cholesterol (LDL-c).<sup>1,2</sup> Even individuals who are hyper-responsive to dietary cholesterol challenge do not present worsening in LDL-c/HDL-c ratio, which is a better predictor of cardiovascular disease than each of them isolated.<sup>3,4</sup> In addition, considering LDL particle sizes, egg intake favors the

change from small-dense LDL pattern (pattern B) to large LDL pattern (pattern A), which are much less susceptible to oxidation and to deposition in vascular wall.<sup>5</sup> Furthermore, adjustment by body weight should also be considered to determine whether obesity was a determinant factor promoting lipid alterations and, consequently, histological findings.

A cheap and efficient option to induce atherosclerosis would be the use of another animal model, for example Hartley guinea pigs.<sup>6</sup> Considering the two most common breeds of both species, the price of each guinea pig is much cheaper than New Zealand white rabbits (from US\$ 46 to 78 for each guinea pig and from US\$ 80 to 169 for each rabbit) in the USA.<sup>7</sup> In addition, the price of feeding guinea pigs is at least comparable to the price of feeding rabbits.<sup>8</sup> For example, in our lab the final cost of the semi-purified diet used to feed one guinea pig with high cholesterol and high carbohydrate diet for 12 weeks was about US\$ 73.5. In the USA, based on a non-enriched chow, the cost of feeding each rabbit would vary from about US\$ 79 to 119 for the same period of time.<sup>8</sup> Hence, in the USA, the combined cost of buying and feeding rabbits is actually higher when compared to guinea pigs.<sup>9,10</sup> It is possible that the costs of buying and feeding guinea pigs are cheaper than rabbits also in Brazil. However, possible variations in price among countries might be expected and should be considered.

In addition to the possible advantages in cost, guinea pigs might be a better surrogate to human atherosclerosis than rabbits. Physiologically, guinea pigs present the

closest lipid metabolism to humans.<sup>6</sup> Most of their plasma cholesterol is carried in LDL, as opposed to rodents and rabbits, which carry most of cholesterol in HDL and very low-density lipoprotein (VLDL) particles, respectively.<sup>6,9</sup> Guinea pigs present similar activities in the major regulators of cholesterol and lipoprotein metabolism, including lecithin:cholesterol acyltransferase (LCAT), cholesteryl ester transfer protein (CETP), acyl-coenzyme A:cholesterol acyl transferase (ACAT), cholesterol 7 $\alpha$ -hydroxylase (CYP7) and 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) compared to humans.<sup>6</sup> They respond very well to cholesterol, carbohydrate, fatty acids, including trans-fatty acids and polyphenols challenge.<sup>6</sup> Because of the aforementioned similarities to humans, guinea pigs have been chosen as the prototype to study drugs that interfere with atherosclerosis and lipid metabolism, for example, HMG-CoA reductase inhibitors, cholestyramine, apical sodium-dependent bile acid transporter (ASBT) inhibitor, microsomal triglyceride transfer protein (MTP) inhibitor and rapamycin.<sup>6,10</sup> Hence, the use of guinea pigs should be considered when the aim is to have diet-induced atherosclerosis.

On the other hand, the great disadvantage of guinea pigs is exactly the biggest strength of rabbits. Whilst the literature considering guinea pigs as surrogate to surgical models is quite little, there is a vast number of experiments using rabbits. These animals became a classic model to study restenosis especially after the development of balloon and wire injury models.<sup>11,12</sup> Therefore, rabbits might be a superior model when the aim is to study intimal hyperplasia or surgical techniques.

Others simple interventions, as described by the authors, could induce atherosclerosis more severely in the rabbit model. An increasing carbohydrate and saturated fat content on chow would be an inexpensive alternative. The corn oil used to enrich the chow could be replaced by coconut oil. The idea would be to replace the oil rich in polyunsaturated fatty acids, which does not accelerate atherosclerotic lesions, by an oil rich in

saturated fatty acids, which is extremely atherogenic, without increasing the costs.<sup>13</sup>

In conclusion, although rabbits are a viable model to study atherosclerosis, other diet compositions or animal models could be used to strengthen the current results.

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### Resposta dos autores

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Prezados Dr. Moura Leite e Dr. Fernandez,

Agradecemos os comentários embasados e pertinentes que fizeram sobre o artigo “Atherosclerotic lesion formation in rabbits fed on egg yolk-supplemented diet: an inexpensive experimental model”, publicado na edição de dezembro de 2006 do *Jornal Vascular Brasileiro*. Tal pesquisa foi realizada no intuito de avaliar a produção de aterosclerose experimental, através de fonte alimentar de colesterol de fácil acesso e baixo custo.

Estudamos a gema de ovo como fonte de colesterol alimentar, pois é um modelo clássico de indução de hipercolesterolemia. Além disso, a hipercolesterolemia alimentar é a via mais prática e difundida na indução de aterosclerose experimental. Ao contrário do afirmado na carta, a Figura 1 do artigo mostra claramente um aumento significativo ao longo do tempo dos níveis sanguíneos de colesterol (LDL-colesterol e HDL-colesterol), exceto triglicérides, nos animais tratados em relação aos controles. Na discussão do artigo, são apontadas estratégias para se provocar hipertrigliceridemia nestes animais.

A espécie escolhida foi o coelho pois este é, indubitavelmente, o animal mais utilizado nos modelos de aterosclerose experimental<sup>1</sup>, e diversos estudos de impacto utilizaram este animal<sup>2,3</sup>. Sua utilização neste caso foi essencial, pois forneceu-nos elementos para comparação de resultados de outros autores. Além

disso, o coelho é facilmente disponível nos biotérios e é usado em boa parte das pesquisas nesta área realizadas em nosso país e no mundo. A sugestão do uso de cabaia com certeza deve trazer contribuição adicional a este tipo de pesquisa. As vantagens apontadas na carta fazem crer que a cabaia passe a ocupar um lugar de crescente destaque neste tipo de pesquisa.

Na discussão do artigo, enfatizamos que as lesões ateroscleróticas observadas em nosso modelo foram similares às obtidas com modelos em que a quantidade de colesterol fornecida, por meio do colesterol comercial, era de 0,15%. Modelos no mesmo animal com ingesta de 1,0% de colesterol na dieta mostraram lesões mais proeminentes. Assim, acreditamos que com fornecimento de maior proporção diária de gema de ovo, conseguiríamos lesões mais importantes sem impacto significativo dos custos, em comparação com o colesterol purificado comercial, este sim, bastante oneroso: note-se que o custo da dieta com gema de ovo foi 81 vezes menor do que seria com colesterol comercial (Tabela 1 do artigo). Outras estratégias para incrementar as lesões foram igualmente apontadas na discussão do nosso trabalho. A sugestão dos missivistas de substituir o óleo de milho por óleo de coco é alternativa bastante atrativa e econômica.

As pesquisas com dietas e modelos de aterosclerose, como apontado na discussão do artigo, tiveram impulso desde o começo do século passado. Até hoje, há uma contínua busca por fórmulas e modelos que mimetizem as condições encontradas em seres humanos, com aplicabilidade e viabilidade. As pesquisas e os trabalhos desenvolvidos fornecem material fértil para discussão, sendo a polêmica e a contestação dos projetos essenciais para o enriquecimento do conhecimento. Agrademos aos autores da carta o interesse pelo tema do artigo e pela oportunidade desta troca de idéias.

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