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Dairy products and the French paradox: Could alkaline phosphatases play a role?

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ABSTRACT

The French paradox – high saturated fat consumption but low incidence of cardiovascular disease (CVD) and mortality – is still unresolved and continues to be a matter of debate and controversy. Recently, it was hypothesised that the high consumption of dairy products, and especially cheese by the French population might contribute to the explanation of the French paradox, in addition to the "(red) wine" hypothesis. Most notably this would involve milk bioactive peptides and biomolecules from cheese moulds. Here, we support the "dairy products" hypothesis further by proposing the "alkaline phosphatase" hypothesis. First, intestinal alkaline phosphatase (IAP), a potent endogenous anti-inflammatory enzyme, is directly stimulated by various components of milk (e.g. casein, calcium, lactose and even fat). This enzyme dephosphorylates and thus detoxifies pro-inflammatory microbial components like lipopolysaccharide, making them unable to trigger inflammatory responses and generate chronic low-grade inflammation leading to insulin resistance, glucose intolerance, type-2 diabetes, metabolic syndrome and obesity, known risk factors for CVD. Various vitamins present in high amounts in dairy products (e.g. vitamins A and D; methyl-donors: folate and vitamin B12), and also fermentation products such as butyrate and propionate found e.g. in cheese, all stimulate intestinal alkaline phosphatase. Second, moulded cheeses like Roquefort contain fungi producing an alkaline phosphatase. Third, milk itself contains a tissue nonspecific isoform of alkaline phosphatase that may function as IAP. Milk alkaline phosphatase is present in raw milk and dairy products increasingly consumed in France. It is deactivated by pasteurization but it can partially reactivate after thermal treatment. Experimental consolidation of the "alkaline phosphatase" hypothesis will require further work including: systematic alkaline phosphatase activity measurements in dairy products, live dairy ferments and intestine of model animals. Furthermore, stool residual IAP, a possible early marker of diabetes, should be assayed in human cohorts. If confirmed, this "alkaline phosphatase" hypothesis will highlight the protective effects of milk alkaline phosphatase and promote the consumption of (microbiologically safe) raw milk and dairy products. Microorganisms secreting alkaline phosphatases may be privileged as ferments in dairy products.

Background

The French paradox comes from the observation that French people consume high amounts of saturated fats but have low cardiovascular disease (CVD) and associated mortality rates. This paradox first defined by Renaud and De Lorgeril in 1992 [1] is still unresolved and subject to debates and controversy. Today, French people still enjoy life expectancy among the longest, especially for women in OECD countries despite higher associated risk factors like smoking and alcohol consumption [2]. For instance, alcohol consumption is still 25% higher in France than in OECD countries (11.1 vs. 8.8 L/capita/year). In line with the French paradox, the percentage of overweight and obese adults is lower in France than in most OECD countries, though it continues to increase over time [2].

The first factor proposed to explain the French paradox was the high consumption of wine in France [1]. This led to identification of (red) wine polyphenols and especially resveratrol as the principle cardio-protective biomolecules, though small amounts of alcohol itself may also be protective [3]. One nearly unanimous conclusion is that moderate consumption of (red) wine has beneficial effects on CVD and other metabolic diseases (e.g. type-2 diabetes mellitus, T2DM), and maybe on neurodegenerative diseases and longevity [4]. However, explanations for the French paradox are obviously multiple, involving not only wine but also other key components

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of French diets and meal patterns. Conversely, confounding factors e.g. linking wine consumption to socio-economic criteria have also emerged [5], illustrating possible biases in past epidemiological studies.

The "dairy products" hypothesis was formulated in *Medical Hypotheses* three years ago as "the missing piece of the French paradox puzzle" [6]. This hypothesis was based on the observation that French people consume a lot of dairy products, and especially cheese (>26 kg/capita/year) [6]. In summary, information was gathered showing that milk-borne bioactive peptides, those inhibiting angiotensin-I converting enzyme and others regulating thrombotic functions, blood coagulation and microcirculation contribute to reduced blood pressure. Other dairy components, e.g. with anti-inflammatory properties may operate too [7,8]. Roquefort, a blue cheese was pointed out as particularly protective due to the presence of bioactive molecules such as androstins A-D and roquefortine [6]. The former are potent inhibitors of the enzyme farnesyl transferase involved in cholesterol synthesis while the latter is antibacterial and inhibits the growth of Gram-positive bacteria. The "dairy products" hypothesis is supported, at least in part by clinical data [9]. However, milk peptides and mould products are certainly not the only bioactive molecules contributing to the explanation of the positive effects of (fermented) dairy products on health.

In the present paper, we hypothesise that dairy products, in addition to aforementioned properties, contribute to the reduction of the risk of metabolic diseases and CVD thanks to their stimulatory effects on intestinal alkaline phosphatase (IAP). IAP is a vital enzyme with multiple physiological functions, the most important with regard to metabolic diseases and CVD being the control of intestinal and systemic inflammation [10,11]. IAP is inhibited by inflammation but is stimulated by diverse dietary components of which many (e.g. casein, calcium, lactose, fat; vitamins A and D; methyl-donors: folate and vitamin B12) are in high concentrations in dairy products. Raw milk and its fractions also contain an isoform of alkaline phosphatase. This enzyme is present in raw dairy products which consumption increases in France. It is inactivated by pasteurization but it can partially reactivate afterwards. Stimulation of endogenous IAP by dairy products together with the presence of milk- or microbe-derived alkaline phosphatases may contribute to the global protective effect of the French regimen characterized with high intake of dairy products. Ironically, alcohol at low concentration stimulates IAP while red wine polyphenols are anti-inflammatory [12,13]. Therefore, the "alkaline phosphatase" hypothesis may well fit to the "(red) wine" hypothesis too.

Recent epidemiological data on the effects of dairy products on health

A body of literature has been generated on the possible associations between the consumption of milk and dairy products and various metabolic and cardiovascular-related diseases. Among dairy constituents, there has been a focus upon fat, calcium and vitamin D and many studies, though not all have reported beneficial associations.

Positive associations between milk consumption and lower body fat, higher glucose tolerance, and lower metabolic syndrome or CVD risks have been documented [14–17]. Yogurt consumption was associated with reduced risks of body weight gain, metabolic syndrome and CVD [15,18–20]. This was so between cheese consumption and lower risk of T2DM, metabolic syndrome, stroke and coronary heart disease (CHD) [21–23]. Cheese is usually rich in fat and dairy fats have been under focus for their effects on health. Despite controversies, recent data support less negative effects of dairy fats than previously anticipated [24,25]. For example, favorable associations were found between the consumption of full-fat dairy products and metabolic syndrome, T2DM, obesity or stroke [21,26–28].

Milk and dairy products are important sources of minerals and vitamins and special attention has been devoted to calcium and vitamin D, often deficient in various at-risk populations (e.g. adolescents) or groups with metabolic syndrome or CVD [15,29,30]. Dairy products and calcium status have been found to inversely correlate with insulin resistance and T2DM, metabolic syndrome, stroke and CVD [31–34]. Importantly, mineral sources of calcium or very high calcium consumption appear to display opposing effects, being reported to positively associate to (e.g. CVD) diseases and mortality [34–36]. Dairy product consumption and vitamin D status are inversely associated with insulin resistance and T2DM [31]. Finally, in two prospective studies vitamin K2 which is present in higher concentrations in fermented dairy foods was shown to reduce the risk of CHD [37,38].

Consistent linear or U-shaped positive correlations have been observed between circulating (plasma or serum) AP activity and increased risks of various diseases, including hypertension, stroke and CVD [39–41]. This may not be surprising because circulating AP may be a marker of inflammation [11].

Intestinal alkaline phosphatase is a potent anti-inflammatory enzyme

The intestinal isoform of alkaline phosphatase (IAP) is an enzyme produced by the enterocyte and is involved in many physiological processes taking place in the intestine and beyond [10,11]. The major property of IAP is its potent anti-inflammatory action. The underlying mechanisms include: (i) IAP dephosphorylation of various pro-inflammatory microbial components, including LPS, thus making them unrecognizable by Toll-Like Receptors (TLR) and preventing the activation of TLR-mediated intracellular NFκB signaling pathway that leads to inflammatory responses by enterocytes and circulating immune cells, and (ii) the direct inhibition of NFκB pathway components by intracellular IAP in enterocytes [10,11]. Importantly, enteric LPS has been demonstrated in animal models to cause low-grade inflammation and associated shifts in metabolic functions, leading to glucose intolerance, insulin resistance, dyslipidemia, metabolic diseases and obesity [42,43]. Remarkably, exogenous (bovine) IAP is able to prevent as well as to treat fat-diet-induced metabolic syndrome in mice [44]. In line with this, rats resistant to fat diet-induced obesity exhibit higher IAP and lower inflammation compared to sensitive rats [45]. All the information available to date indicates that exogenous IAP administration is effective in treating diverse inflammatory diseases such as inflammatory bowel disease and acute or chronic kidney disease in animal models and humans [11]. Collectively, both experimental and clinical observations support the notion that IAP is a key anti-inflammatory enzyme able to control both gut and systemic inflammation.

Many milk and dairy components stimulate intestinal alkaline phosphatase

Various milk components, including casein, calcium and lactose all have been shown to stimulate IAP activity in rats [10]. Data with fermented dairy products are scant but yogurt has been shown to enhance jejunal IAP activity while calcium added to milk or yogurt is protective against infectious enteritis in rats [46].

Dietary fat is also a strong stimulator of IAP [10,11]. Lipopolysaccharide which is lipid-soluble enters the body at the intestinal level together with long-chain fatty acids through chylomicrons [47]. Long-chain fatty acids do stimulate IAP activity.