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## Review

# Influence of Amino Acids in Dairy Products on Glucose Homeostasis: The Clinical Evidence

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## ABSTRACT

Dairy products have been hypothesized to protect against type 2 diabetes because of their high content of whey proteins, rich in branched-chain amino acids (BCAAs) - leucine, isoleucine and valine - and lysine, which may decrease postprandial glucose responses and stimulate insulin secretion. Paradoxically, epidemiologic studies also show that higher levels of plasma BCAAs have been linked to insulin resistance and type 2 diabetes. Therefore, the objective was to review the recent clinical evidence concerning the intake of amino acids found in dairy proteins so as to determine their impact on glucose homeostasis in healthy persons and in those with prediabetes and type 2 diabetes. Clinical studies have reported that the major dairy amino acids, namely, leucine, isoleucine, glutamine, phenylalanine, proline and lysine, have beneficial effects on glucose homeostasis. Yet the reported doses of amino acids investigated are too elevated to be reached through adequate dairy product intake. The minor dairy amino acids, arginine and glycine, may improve glucose homeostasis by improving other risk factors for type 2 diabetes. Further, the combination of amino acids may also improve glucose-related outcomes, suggesting additive or synergistic effects. Nevertheless, additional long-term studies in individuals with prediabetes and type 2 diabetes are needed to ascertain the benefits for glucose homeostasis of amino acids found in dairy foods.

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## R É S U M É

D'aucuns soutiennent que les produits laitiers protègent contre le diabète de type 2 en raison de leur teneur élevée en protéines lactosériques, riches en acides aminés à chaîne ramifiée (AACR), la leucine, l'isoleucine et la valine, et en lysine, qui peuvent diminuer les réponses glycémiques postprandiales et stimuler la sécrétion d'insuline. Paradoxalement, les études épidémiologiques montrent également que des concentrations plasmatiques plus élevées en AACR sont associées à l'insulinorésistance et au diabète de type 2. Par conséquent, l'objectif était de passer en revue les récentes données cliniques au sujet de l'apport en acides aminés observé dans les protéines du lait de façon à déterminer leurs effets sur l'homéostasie glucidique chez les personnes en bonne santé et chez les personnes atteintes du prédiabète et du diabète de type 2. Les études cliniques ont rapporté que les acides aminés majeurs des produits laitiers, à savoir la leucine, l'isoleucine, la glutamine, la phénylalanine, la proline et la lysine, ont des effets bénéfiques sur l'homéostasie glucidique. Cependant, les doses d'acides aminés étudiées qui ont été rapportées sont trop élevées pour être atteintes par un apport adéquat en produits laitiers. Les acides aminés mineurs des produits laitiers, à savoir l'arginine et la glycine, peuvent améliorer l'homéostasie glucidique en améliorant d'autres facteurs de risque du diabète de type 2. De plus, la combinaison des acides aminés peut aussi améliorer les résultats de glycémie, ce qui suggère des effets additifs ou synergiques. Néanmoins, d'autres études à long terme chez les individus atteints du prédiabète ou du diabète de type 2 sont nécessaires pour déterminer les avantages de l'homéostasie glucidique des acides aminés observés dans les aliments à base de lait.

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## Introduction

Type 2 diabetes is characterized by hyperglycemia that is triggered by impaired production of or use of insulin. This chronic disease affected 285 million adults in 2010 and is expected to reach 439 million adults by 2030 (1). Prediabetes is defined by impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) with elevated glycated hemoglobin (A1C) levels and is a major risk factor for the development of type 2 diabetes (2). Accordingly, normalizing plasma glucose concentration through plasma insulin and glucagon management is critical in order to prevent type 2 diabetes and its long-term vascular and renal complications. Specifically, a healthful diet and increased physical activity remain the cornerstones of the management of plasma glucose levels.

Epidemiologic studies report that dairy product consumption is associated with improved glucose metabolism and a lower risk for type 2 diabetes (3–5). Among milk bioactive nutrients, dairy proteins, caseins and whey proteins and their derived peptides have been shown to improve several metabolic parameters. Specifically, clinical studies and reviews have reported that dairy proteins increase satiety, decrease postprandial glucose responses and stimulate insulin secretion and, thus, may prevent people from the development of type 2 diabetes (6,7).

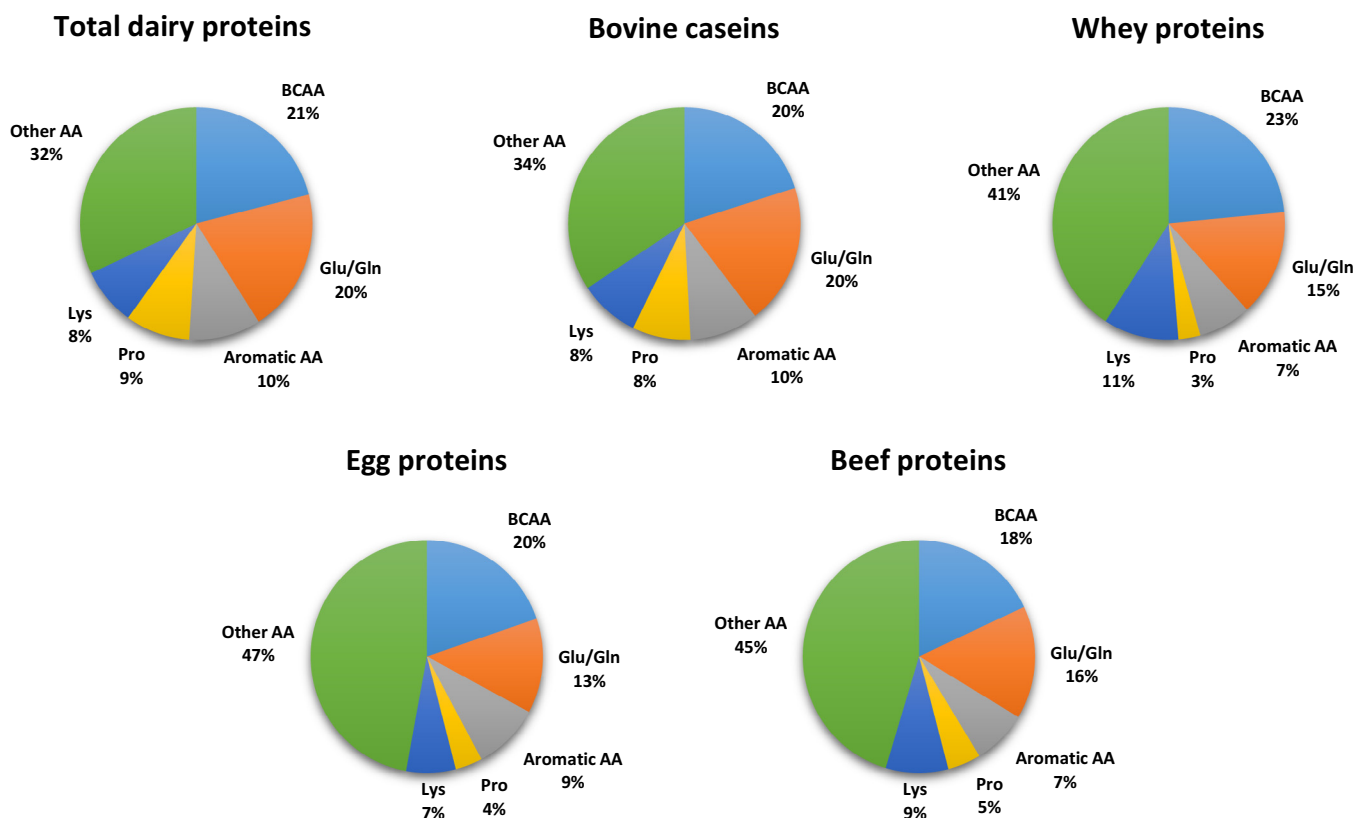
The beneficial effects of dairy proteins on glucose homeostasis may be due, in part, to their amino acid profile (Figure 1). Bovine milk proteins, especially whey proteins, are rich in essential amino acids, specifically, branched-chain amino acids (BCAAs) - leucine, isoleucine and valine - and lysine. The proportion of BCAAs is 23% and 20% in whey proteins and caseins, respectively. Specifically, whey proteins have a higher proportion of leucine (12%) than caseins (8.5%) (8). Caseins are characterized by higher proportions of nonessential

amino acids, glutamic acid, glutamine and proline. Dairy proteins also contain the aromatic amino acid residues, phenylalanine and tyrosine. In sum, BCAAs, lysine, glutamic acid, glutamine, proline and aromatic amino acids represent approximately 70% of the total amino acid residues in bovine milk proteins (8). Plasma concentrations of BCAAs and aromatic amino acids have been associated with insulin resistance and type 2 diabetes. Because dairy products are an important source of proteins and, hence, of amino acids, understanding the role played by amino acids, especially BCAAs, in glucose management could prove valuable. The purpose of this article is to review the recent clinical evidence of the effects of specific amino acids found in bovine milk proteins, as well as their combinations, on glucose homeostasis in healthy people and in those with prediabetes and type 2 diabetes.

Human clinical studies published between 2000 and 2015 were included in this review if they evaluated the effect of an oral amino acid supplementation on various key outcomes implicated in type 2 diabetes management, such as fasting as well as levels of postprandial plasma glucose, plasma insulin, plasma glucagon, insulin resistance, A1C and other pertinent type 2 diabetes risk factors. Additionally, in order to determine whether the doses investigated are reachable via the current daily recommendation of dairy product intake, we compared the dose of amino acid supplemented to the dose provided by a single 250 mL portion of 2% fat milk, 175 grams of yogurt and a 250 mL portion of cottage cheese.

## BCAAs

Dairy proteins contain about 21% of BCAA residues, including leucine, isoleucine and valine (Figure 1). BCAAs are involved in metabolic pathways regulating muscle protein synthesis and, thus, are



**Figure 1.** Proportions % w/w of total amino acids of differing classes of amino acids found in animal proteins, including total dairy proteins, bovine caseins and whey proteins (adapted from reference 8) as well as egg proteins and beef proteins using the Canadian nutrient file (<https://food-nutrition.canada.ca/cnf-fce/index-eng.jsp>). Egg, food code: 83; beef, food code: 6172. AA, amino acid; BCAA, branched-chain amino acids; Glu/Gln, Glutamic acid/Glutamine; Lys, Lysine; Pro, Proline.

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