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Title: The protective effect of raw cow's milk in allergy can be explained by the presence of high levels of aeroallergen-specific IgGs.

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Background: Over the last 20 years, evidence has been accumulating that growing up on a farm is associated with a decreased prevalence of asthma and rhinitis. This effect is linked to the consumption of unprocessed raw cow's milk and to microbial exposure. The effect of farm milk consumption is only seen when the farm milk is not heated, suggesting that it is linked to the presence of non-denatured milk proteins. Cow's milk contains immune regulatory components such as immunoglobulins, especially IgG, lactoferrin, TGF- β .

Hypothesis: Allergen-specific IgGs in unprocessed milk consumed at farms is present for the most common aeroallergens and these sIgGs can block allergen-mediated activation of effector cells as well as CD23-mediated facilitated antigen presentation.

Aim: The presence of aeroallergen-specific IgGs was determined in colostrum, unprocessed milk, pasteurized milk and sterilized milk. The functional effects of these IgGs will be tested on the binding of house dust mite (HDM)-IgE immune complexes to CD23-expressing B cells, as well as their blocking effects in HDM-induced basophil activation in BAT.

Approach: The presence of IgG was determined in different unprocessed and processed cow's milk products by the EUROLINE inhalation membrane strips (EUROIMMUN AG) and alkaline phosphatase-labeled anti-bovine IgG. The binding of immune complexes of serum IgE with house dust mite allergens (ALK, Denmark) to CD23-expressing B cells was determined using flow cytometry.

Results: In colostrum, raw milk products and commercially available pasteurized cow's milk IgGs were present in high amounts against the mites *D. farinae*, *D. pteronyssinus*, the fungi *A. alternata*, *A. fumigatus*, *C. herbarum* and *P. notatum*, sweet vernal, orchard, timothy and cultivated rye grasses, hazel tree pollen and ragweed. Some moderate sIgG levels were found for alder, birch and oak tree pollen and mugwort and English plantain. No sIgG were detected for cat, dog or horse allergens. The highest level for sIgG was demonstrated in colostrum. The sIgG level in raw milk differed between different farms but was comparable to that found in pasteurized cow's milk. Commercially available sterilized (Ultra-high temperature treated) cow's milk was completely missing any sIgGs for the aeroallergens tested. The binding of house dust mite-IgE complexes was shown for 5 HDM allergic donors. Although values were generally slightly lower, preincubation with bovine IgG had no significant blocking effect on the binding of IgE immune complexes to CD23-expressing B cells.

Conclusion: Cow's milk contains significant levels of IgGs against the most common aeroallergens, which are lost after sterilization. This might explain the decreased allergy prevalence associated with raw milk consumption. Even though these do not compete significantly with allergen-specific IgE, they are known to bind to human Fc γ R2 and may have immunomodulatory effects yet to be explored. Further studies will examine the functional properties of these allergen-specific IgGs in blocking allergen-mediated basophil activation.