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Commentary

Intestinal Alkaline Phosphatase in Stool: A Novel Biomarker for Metabolic Diseases

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The epidemic of metabolic disorders, including insulin resistance, type 2 diabetes mellitus (T2DM) and obesity is observed in both developed and developing countries. It now affects all age categories and is often associated in the context of low physical activity with chronic intake of unbalanced (Western) diets characterized by high fat, sugars and low fiber. Western diets are invariably related to gut dysbiosis (e.g. as in obesity), and a higher intestinal translocation of pro-inflammatory microbial components like lipopolysaccharide into the systemic circulation is promoted, thus leading to chronic low-grade systemic inflammation and metabolic shifts towards higher body fat accumulation that ultimately results in the metabolic syndrome and diabetes.

Many data indicate that intestinal alkaline phosphatase (IAP), an enzyme isoform uniquely secreted by enterocytes, consistently reduces inflammation in animal models and in diseases (e.g. in ulcerative colitis, peritonitis, sepsis and heart surgery) in man (Lallès, 2014). Malo and coworkers at Harvard University have previously demonstrated that endogenous, as well as exogenous (bovine) IAP taken orally can prevent, and treat, fat-diet induced metabolic syndrome and T2DM in mice (Kaliannan et al., 2013). This group has also published other decisive papers showing intimate cross-regulation between the gut microbiota and IAP in mice, clearly revealing this enzyme as a potent regulator of inflammation and gut microbiota homeostasis (Lallès, 2014). Data on IAP are scant in humans. In a paper recently published in *EBioMedicine*, Malo now reports for the first time that fecal IAP (fIAP) and T2DM status were independently and negatively associated, both in male and female adults, in a T2DM case–control study conducted in Bangladesh (Malo, 2015). Even more importantly, Malo noted that fIAP was low in 65% of control subjects and suggested fIAP as a possible biomarker for "incipient metabolic syndrome" including "incipient diabetes" in healthy subjects (Malo, 2015). Collectively, these new data perfectly fit with all that is now known on IAP and inflammation (Lallès, 2014). IAP is specifically inhibited by L-phenylalanine allowing it to be distinguished from microbial AP. fIAP and microbial AP account for 80 and 20%, respectively of total stool AP activity in humans and for 60 and 40% in rodents (Malo, 2015; Kim et al., 1986). IAP oral administration was shown to increase fIAP dose-dependently in mice (Lallès, 2014).

This new study by Malo is potentially important as it proposes fIAP as a biomarker of T2DM (and metabolic diseases). However, caution should be taken in evaluating an individual value in the context of confounding factors that modulate IAP. fIAP was first characterized as a marker of intestinal epithelial damage (Thomas & Henton, 1985). In addition, changes in food intake per se could explain most of the effects assigned to other factors, and indeed, enteral feeding is recognized as a major driver of intestinal production and fecal release of IAP (Lallès, 2014; Thomas & Henton, 1985). Further, many dietary components (e.g. fat, the anti-inflammatory spice curcumin and minerals), and also antibiotics and other drugs (e.g. protease inhibitors), alcohol and laxatives are known to modulate fIAP (Lallès, 2014; Ghosh et al., 2014; Davis, 2003; Wu et al., 2010; Hufnagel et al., 1980; Taché et al., 2006). Thus, in the case of an individual, fIAP data needs to be interpreted in light of these dietary factors and treatments.

In conclusion, these data by Malo showing an association between fIAP and T2DM, and also suggesting "incipient T2DM" in (apparently) healthy subjects based on fIAP values, are very interesting. However, any individual IAP value should be evaluated in the context of associated factors modulating fIAP.

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