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Manipulating dietary fibre: Gum Arabic making friends of the colon and the kidney


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There is an appreciation that the incidence of chronic renal disease is increasing worldwide. This is a health issue, which carries significant morbidity and mortality for patients. Furthermore treatment of patients with renal failure is expensive and therefore represents a significant financial burden to health economies. This review provides an overview of the in vitro, in vivo and clinical evidence supporting the potential therapeutic benefit of manipulating dietary fibre intake and specifically supplementation of the diet with Gum Arabic in patients with progressive renal disease.
1. Dietary fibre and disease

Dietary interventions have been an important cornerstone of medicine since its early days. Epidemiological evidence suggests that a high intake of dietary fibre is associated with numerous health benefits, with reduced mortality documented in those consuming a diet rich in whole grain (Jacobs, Meyer, & Solvoll, 2003). High intake of fibre from cereals and high consumption of wholegrain foods is significantly associated with a reduced risk of colorectal cancer (Aune et al., 2011). Observational studies also suggest that a diet high in fibre may confer protection from the risk of cancers beyond the colon (La Vecchia, Chatenoud, Negri, & Franceschi, 2003), which suggests systemic beneficial effects. This is further supported by evidence of the potential favourable effect of whole-grain foods on cardiovascular disease (Truswell, 2002), and the risk of myocardial infarction (Rimm et al., 1996). Studies on the consumption of whole grains and the risk of type 2 diabetes together with observational studies demonstrating an inverse association between fibre intake and the occurrence of type 2 diabetes also suggest a role for fibre supplementation in the prevention of type 2 diabetes, possibly associated with a lower incidence of obesity (Cho, Qi, Fahey, & Klurfeld, 2013). More recent studies suggest that a high dietary fibre intake may also provide clinical benefit for patients with chronic kidney disease (Krishnamurthy et al., 2012). Chronic renal disease represents an expensive and rapidly growing health issue. Its incidence is increasing with current estimates that up to 10% of the population have impaired renal function (Coresh et al., 2007).

2. Regulatory definition of dietary fibre

The Codex Committee on Nutrition and Foods for Special Dietary Users finally agreed an internationally acceptable definition of dietary fibre in 2009 (Phillips & Cui, 2011). The question was – should it be defined according to its chemical category or its physiological function. The following chemical definition was finally adopted:

"Dietary fibre means carbohydrate polymers with 10 or more monomeric units which are not hydrolysed by the endogenous enzymes in the small intestine of humans and belong to the following categories:

- edible carbohydrate polymers naturally occurring in the food as consumed;
- carbohydrate polymers, which have been obtained from food raw material by physiological, or chemical means and which have been shown to have a physiological effect or benefit to health as demonstrated by generally accepted scientific evidence to competent authorities; and
- synthetic carbohydrate polymers which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities" (Cummings & Stephen, 2007).

It is not clear whether it is the chemical characterisation or its physiological action which are the critical factors. Conversion in the colon to short-chain fatty acids is a necessary requirement if the material is to be accepted as a dietary fibre. But to make a health claim it also needs biological, physiological and clinical evidence and chemical characterisation of the test material. Therefore while the general identification of dietary fibre can be made on a chemical basis, any specific health claim must be based upon its physiological and clinical performance (Phillips, 2013).

3. Dietary fibre and renal disease

In patients with chronic kidney disease (CKD), dietary advice currently focuses on the intake of salt, phosphate, potassium and protein. The role of dietary fibre is less well defined. Fruits and vegetables, often restricted in CKD to prevent or correct hyperkalaemia, are an important source of dietary fibre. In patients with CKD dietary fibre intake is therefore known to be well below the recommended daily intake of 25–30 g/day (Kalantar-Zadeh, Kopp, Deepak, Block, & Block, 2002; Krishnamurthy et al., 2012). There are studies which date back over 25 years which suggest that modification of fibre intake may have beneficial effects on renal function. In an animal model of diabetic renal disease a high fibre diet was associated with amelioration of the pathological changes within the kidney (Lee, 1982). In human studies, locust bean gum, a non-digestible polymer of mannose and galactose derived from the seeds of the ceratonia siliqua tree, has been demonstrated to be an efficient sorbent which binds to many of the potential toxic substances found in patients with chronic renal failure (Yatzidis, 1977). In a study of only two patients, it was also suggested that dietary supplementation with locust bean gum improved both blood pressure control and also reduced serum creatinine (Yatzidis, Koutsicos, & Digenis, 1979). These observations, which have not been investigated further, and if confirmed would suggest a mechanism other than that related to its “sorbent” properties by which locust bean gum may influence progressive renal disease. In addition, a case report of a single patient, using dietary supplementation with the hemicellulosic ispaghula husk also suggested a beneficial effect on renal function beyond increased faecal bacterial loss (Rampton et al., 1984). A recent landmark study however has reignited interest in the role of dietary fibre in renal disease demonstrating in a large observational study using the Third National Health and Nutritional Examination Survey (NHANES III), a data base over 14,500 participants, which identifies a positive association between fibre intake and mortality in patients with kidney disease (Krishnamurthy et al., 2012).
4. Dietary fibre, is there a mechanistic basis for the health claims?

Evidence of association as described above is clearly not proof of causation, and even the most rigorous observational studies may be subject to confounding bias. Ideally randomized controlled trials are needed to provide proof of principle and provide evidence of causation. In the absence of such large-scale studies there is experimental evidence which provides a mechanistic basis by which altering fibre intake may affect the progression of renal disease. In particular it has been proposed that the beneficial effects of dietary fibre may be mediated by modification of colonic microbial metabolism. In evolutionary terms the colonic microbiome’s principal function is to extract energy from plant polysaccharides that cannot be digested by host enzymes, a source of energy which is relatively redundant with the consumption of a modern day “industrialised” diet. The action of colonic bacteria, however, results in the generation of numerous compounds, the excretion of which occurs through the urine. Colon-derived solutes therefore accumulate in the blood of patients with chronic renal failure. Evidence is emerging that these products of colonic bacterial action contribute to progression of renal disease, and may provide a potential therapeutic target that may be manipulated by nutritional therapy.

The colon-derived uraemic solutes most extensively investigated are indoxyl sulphate and p-cresyl sulphate. This focus is mainly because they are formed in relatively large quantities, but it is likely that other colon derive uraemic solutes which accumulate at lower concentrations may also be significant contributors to disease pathogenesis.

There is mounting evidence indicating that indoxyl sulphate contribute to progression of renal disease. Serum levels rise in parallel to the loss of kidney function (Wu et al., 2011). Both animal experiments and in vitro cell culture work also support a role of indoxyl sulphate in perpetuating a profibrotic response driving a progressive decline in renal function (Miyazaki et al., 1997; Miyazaki, Ise, Seo, & Niwa, 1997). Similarly evidence is mounting that p-cresyl sulphate serum concentrations are independently associated with overall mortality and are an independent predictor of incident cardiovascular disease in haemodialysis patients (Sammens, Evenepoel, Keuleers, Verbeke, & Vanreentghem, 2006; Meijers et al., 2008). Mechanistically in vitro studies have demonstrate activation of leucocytes by p-cresyl sulphate (Scheipers et al., 2007), an important finding as CKD is considered to be an inflammatory state, with raised inflammatory markers being predictors of cardiovascular events and mortality.

Reducing the load of colon-derived solutes has been postulated to be a potential therapeutic option in CKD to both delay progression of renal disease and also to reduce the associated cardiovascular morbidity and mortality. One such approach is to administer sorbents that bind to microbial metabolites. Evidence is accumulating that the carbon-based sorbent AST-120 may reduce circulating levels of indoxyl sulphate and ameliorate decline in renal function (Iida et al., 2006; Nakamura et al., 2011; Owada et al., 2010; Ueda, Shibahara, Takagi, Inoue, & Katsuoka, 2007, 2008). This reduces the intestinal absorption of tryptophan-derived indoles, which subsequently reduces the hepatic conversion of indoles to indoxyl sulphate.

Patients with CKD are faced with a high burden of intake of medication, and therefore a potentially more acceptable approach may be to the limit of the production of colon-derived solutes by dietary manipulation. Industrialised diets contain relatively low levels of fibre which is further reduced in patients with CKD due to the dietary restriction that patients face to limit potassium intake. With limited substrate for fermentation, microbial growth reduced and the volume of stool, of which microbes make up a major portion, is reduced. The amount of amino acids needed for synthesis of microbial protein is thus reduced, so that an increased portion of the protein and peptides delivered to the colon is converted into uraemic solutes. Increasing dietary fibre intake is predicted to have the opposite effect and to limit the conversion of amino acids to uraemic solutes while increasing microbial growth. Dietary fibre also shifts the colonic microbial activity from a proteolytic towards a saccharolytic fermentation pattern. This end result of a high fibre diet is therefore decreased generation of indoles and phenols, which potentially limits progression of renal disease. The recent data derived from the NHANES III survey supports this hypothesis and was particularly notable in that the beneficial effect of high dietary total intake and mortality is strongest in patients with kidney disease, and if fact was not associated with mortality in patients without renal disease (Krishnamurthy et al., 2012). This large population-based observational study therefore suggests that the presence of chronic kidney disease is a potent modifier of the beneficial effects of dietary fibre intake.

A second mechanism by which dietary fibre is postulated to provide health benefit in through the production of short chain fatty acids, as a product of fibre fermentation, since SCFA are known to have a host of biologically important effects including modulation of cell proliferation, apoptosis, regulation of angiogenesis and inflammation (Smith, Yokoyama, & German, 1998). These effects of SCFA have been linked to the improvement of both colonic and systemic health. Our in vitro work related to the pathogenesis of progressive renal fibrosis suggests that SCFA also have antifibrotic activities both reducing the generation and the biological activity of the key pro-fibrotic cytokine Transforming Growth Factor-β1 (TGF-β1) (Matsumoto et al., 2006). Suppression of activity of this cytokine is an important finding as it has been implicated in triggering the final common pathway across a host of renal diseases, which eventually results in end-stage renal failure. This therefore suggests a second mechanism by which dietary manipulation of fibre intake may be used as a therapeutic tool in CKD in addition to its effect on the generation of uraemic retention solutes. It is of note however that the amount and type of SCFA formed by colonic bacteria depend on the chemical structure, composition and amounts of the available substrate. This has important implications such as health benefit claims cannot be assumed to be generic for all types of fibre. One particular dietary fibre which has generated interest in the context of CKD is Gum Arabic.
5. Gum Arabic (Acacia senegal)

Gum Arabic (GA) is an edible tree gum exudate, which has an important and widespread industrial use as a stabiliser, thickening agent and emulsifier, mainly in the food industry, but also in the textile, pottery, cosmetic and pharmaceutical industries. It has been extensively tested for its properties as non-digestible polysaccharide. Gum Arabic (GA) has been shown to conform to the definition of dietary fibre adopted by Codex, as a non-starch polysaccharide, since GA is not digested in the intestine but is fermented in the colon to give short-chain fatty acids, leading to a wide range of potential health benefits. The definition of Gum Arabic allows for the two species Acacia senegal and Acacia seyal. Due to its variable geographical distribution across the Sahelian belt of Africa the commercial product can show extremely wide chemical and physical variability (Idris, Williams, & Phillips, 1998; Mocak et al., 1998).

Because of its physical properties, it retards glucose absorption, increases stool mass, and traps bile acids and has a potential to beneficially modify the physiological status of human subjects (Adiotomre, Eastwood, Edwards, & Brydon, 1990; Annison, Trimble, & Topping, 1995). Therefore, since gum acacia conforms to the chemical definition and can reach the large intestine without digestion in the small intestine, it can be categorised as a non-digestible carbohydrate or dietary fibre. It is fermented by intestinal bacteria to short-chain fatty acids (SCFA) in the large intestine (Adiotomre et al., 1990; Annison et al., 1995; May, Mackie, Fahey, Cremin, & Garleb, 1994). Gum acacia has been shown to be a bifidogenic dietary fibre (Cherbut, Michel, Raison, & Kravtchenko, 2003; Michel et al., 1998). It is able to selectively raise the proportions of lactic acid bacteria and bifidobacteria in healthy subjects. It is fermented slowly, produces short-chain fatty acids and the faecal digestibility is around 95%. It also increases stool output by augmenting the water content of stools. In addition its intestinal tolerance is excellent and high daily doses can be consumed without any adverse intestinal events. All these properties would support a potential role for dietary supplementation with Gum Arabic in renal disease by changing the proteolytic to saccharolytic fermentation pattern of colonic bacteria as outlined above.

6. Gum Arabic in renal disease

In “folk/traditional” medicines GA has many associated claimed health benefits, including beneficial effects for the kidney, and it is widely used in this context in the Middle Eastern and African countries. The renal effects of Gum Arabic are however ill-defined. A reduction of serum urea due to increased bacterial nitrogen excretion in the faeces was reported almost 20 years ago in a cohort of patients with chronic renal disease, providing an additional approach to lowering serum urea nitrogen. Further evidence favouring a positive effect in renal disease was also provided by the work performed over 10 years ago in Khartoum, suggested beneficial effect on blood biochemistry following dietary supplementation with 50 g/day in patients with CKD predominantly undergoing renal replacement therapy (Suliman, Hamdouk, & Elfaki, 2000). A similar finding has more recently been reported from the Central Sudan in a cohort of patients undergoing regular haemodialysis in which supplementation with 50 g/day of Gum Arabic led to an improvement of their biochemical profile (Ali, Ali, Padilla, & Khalid, 2008). In view of the relatively poor status of the health care system in the developing world, this approach may offer a potential supplementary therapy which when combined with dialysis reduces its cost burden and improve patient symptomatology and well-being. Work undertaken in experimental animal models of progressive renal disease suggests that Gum Arabic may also have a direct effect in modifying renal disease prior to the need of renal replacement therapy. Specifically Gum Arabic supplementation (7.5 g/100 ml in drinking water) in a rat model of acute nephrotoxic (gentamicin) renal failure led to a reduction in renal injury independently of its action of faecal bacterial ammonia metabolism (Ali, Al-Qarawi, Haroun, & Moussa, 2003). This direct renoprotective effect of Gum Arabic is supported by observations in models of cisplatin-induced renal injury (Al-Majed, Abd-Allah, Al-Rikabi, Al-Shabanah, & Mostafa, 2003) and a model of ischaemic acute renal injury (Mahmoud, Diaia, & Ahmed, 2012). The experimental evidence in models of chronic renal injury is less clear with studies showing both positive and negative findings in two different rodent models of progressive renal injury (Ali et al., 2010; Ali, Alqarawi, & Ahmed, 2004).

Most previous studies on gum arabic have not specified its species nor its molecular parameters of the material used. Previously we have demonstrated the wide variation in molecular composition, which can result from its geographical origin, age of the tree and nature of the soil, etc. (Al-Assaf, Phillips, & Williams, 2005). A random commercial product too may contain more than one species of acacia. With this in mind we have embarked on the clinical program of work to evaluate the potential health benefits using well characterised and standardised preparations of Gum Arabic, notably A. senegal var senegal using the material, the structure of which was recently described (Shao-Ping et al., 2013). Our recent work, using this well characterised and standardised preparation, demonstrated that dietary supplementation with Gum Arabic has a significant effect on blood pressure in a cohort of patients with renal disease (Glover, Ushida, Phillips, & Riley, 2009), although how this may translate into alterations in renal function in the longer term remains to be determined and is now the focus of ongoing clinical trials.

References


