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Role of Fermentable Carbohydrate Supplements in the Course of Uremia

Hassan Younes

*Institut Polytechnique Lasalle Beauvais
France*

1. Introduction

During the past few years, considerable attention has been given to the impact of nutrition on kidney disease. Interventions that restrict protein intake lower the plasma urea concentration, alleviate adverse clinical symptoms, and may slow the progression of chronic renal failure (CRF). Although these studies provide a logical explanation for a relationship between a low protein diet and altering the progression of functional renal deterioration, this beneficial effect is often accompanied by some muscle wasting and malnutrition. The question arises whether the effect of a moderate dietary protein restriction could be reinforced by enrichment of the diet with fermentable carbohydrates, since these carbohydrates may stimulate the extra-renal route of nitrogen (N) excretion, via the fecal route.

At a physiological level, there is two routes to eliminate N: urine and feces. Our results show that it is possible to increase the N fecal route excretion by reducing the protein supply and increasing fermentable carbohydrate availability. This additional dietary manipulation seems to be very interesting in case of renal deficiency in animal models and in humans. The modification of the urea N enterohepatic cycling by fermentable carbohydrates is likely to promote proliferation of the large intestine microflora, which could be an interesting approach to deviate a part of the N excretion to feces as a consequence of N utilization by the bacteria. Conversely, a large proportion of the N released by urea hydrolysis in the digestive tract may be recycled, via the reabsorption of ammonia, and could contribute thus to reduce the need of N.

In the domain of preventive nutrition, the first recognized effect of dietary fibers was to regularize the digestive transit, especially in the case of constipation. However, during the past decades, some other interesting effects have been reported, especially lipid-lowering effects, improvement of blood glucose control, reduction of colon cancer risk and increase of the availability of some cations. In contrast, the efficacy of the dietary fibers in the treatment of CRF has been less investigated although the availability of dietary fibers should profoundly alter the microflora metabolism and proliferation, and as a result N metabolism.

The aim of this chapter is to review, for the course of CRF, the capacity of an additional manipulation of diet in increasing fermentable carbohydrates which can stimulate the transfer of urea into the large intestine and shift N excretion from the urine to the feces.

2. Relationship between fermentable carbohydrate intake and symbiotic fermentations in the large intestine

Originally, fiber was defined to be the components of plants that resist human digestive enzymes, a definition that includes lignin and polysaccharides (cellulose, hemicellulose, pectin). The definition was later changed to also include resistant starches, along with inulin and other oligosaccharides. Pectin is 90 -100% degradable (by the bacteria in the colon), hemicellulose is 50-80%, and cellulose is 30-50%. Lignin is completely indigestible. Therefore, depending on the concentration of these components in the fiber, the digestibility and calorie value of fiber food varies (Anderson et al., 2009; Cummings et al., 2009).

There is now substantial evidence that fermentative processes similar to those occurring in non-ruminant herbivorous and omnivorous species also take place in the human large intestine (Cummings, 1984; Macfarlane & Macfarlane, 2009). In many animal species, the colon has an important digestive role to recover energy from non-available dietary carbohydrates that are not hydrolyzed and absorbed in the upper digestive tract. Traditionally, the human large intestine has been considered of as an organ that conserves minerals and water, and controls the disposal of indigested products. In recent years, research has also focused on the metabolic and digestive effects of various dietary fibers. In humans, it has been shown that the development of symbiotic fermentations had beneficial effects via the absorption and the utilization of short-chain fatty acids (SCFAs) (Macfarlane & Cummings, 1991; Elia & Cummings, 2007).

The breakdown of nutriment transferred from the ileum into the large intestine is carried out by diverse population of bacteria. In fact, bacteria are ubiquitous in the digestive tract, but the main part of them is confined in the large intestine. In humans, there are from 10^{11} to 10^{12} germs/g of content which are divided up into no less than 400 various species, this represents 35 to 55% of the digestive contents weight (Stephen & Cummings, 1980). This flora, mainly anaerobic, establishes relationships of symbiosis with the host. In addition, they probably fulfill a protective effect towards pathogenic species. The principal substrates for the bacteria are dietary fibers (non-starch polysaccharides, 10 to more 50 g/day), resistant starches (8 to 40 g/day) and oligosaccharides, and as well as proteins. Concerning the quantity of mucus (coming from the higher parts of the digestive tract or secreted in "situ") and the sloughed epithelial cells, there is still an uncertainty about their quantitative contribution.

In humans, the major end-products of carbohydrate breakdown are SCFA (essentially acetate, propionate and butyrate), and the gases H_2 and CO_2 (Fig. 1). The total concentration in SCFA is relatively stable in the large intestine: in the proximal part (cecum, proximal colon), they are generally found in the range of 80 to 150 mmol/L and, in the distal colon, they may be lower (from 50 to 100 mmol/L) (Macfarlane & Cummings, 1991). The SCFA are the main anions in the large intestine. For some osmotic reasons, it is expectable that they could hardly exceed 130-150 mmol/L. However, when the pH of fermentation is very acid (close to 5), the proportion of SCFA under protonated form becomes very important and then, it is possible to find concentrations higher than 150 mmol/L for SCFA alone or, more often, for SCFA + lactate (Macfarlane & Cummings, 1991).

The availability of fermentable carbohydrate influences the molar proportions of SCFA in the colon. Schematically, fermentations with a pH higher than 6.5 are relatively slow and favor the production of acetic acid. Fermentations close to a pH 6.0-6.5 are generally favorable to high propionic acid fermentations, while acidic fermentations (close to 5.5) give

rise to the appearance of notable concentrations of lactate. Other products of the fermentation include branched-SCFA from the deamination of branched-chain amino acids, ammonia, various carboxylic and phenolic acids, and amines (Cummings & Macfarlane, 1991). The branched-SCFA (isobutyrate, isovalerate, 2-methylbutyrate) are very low in the proximal part of the large intestine (less than 10% of the total SCFA) where takes place a very active bacterial anabolism. In the distal part of the large intestine, the exhaustion of fermentable carbohydrates and the rise of the luminal pH favor proteolysis which chiefly affects bacterial protein, together with desaminations of AAs and production of the branched-SCFA. In humans, these last could be 35-40% of the total SCFA in the distal colon (Macfarlane & Cummings, 1991; Tarini & Wolever, 2010).

Fig. 1. Conversion stages of polysaccharides in SCFAs and other fermentation products by microflora in the large intestine

On the other hand, active fermentation stimulates the bacterial growth and leads to a considerable enlargement of the colonic contents and an hypertrophy of the cecal wall in rat (Levrat et al., 1991; Younes et al., 1995a). These changes results in an enlargement of the exchange surface area between blood and the luminal fluid, together with an increase of colonic blood flow. This in turn stimulates the exchanges of urea and ammonia N between blood and digestive lumen (Rémésy & Demigné, 1989; Levrat et al., 1991; Younes et al., 1995b; 1997). The relative hypertrophy of the cecal wall in rat fed fermentable carbohydrates can be ascribed to high concentrations of SCFA, especially butyrate, which is considered as a particularly potent trophic factor (Young & Gibson, 1995; Canani et al., 2011). In this view, it must be noticed that resistant starch exerts a marked trophic effect on colonic mucosa (Demigné & Rémésy, 1982; Bauer-Marino et al., 2006). Data on the action of fiber on colonic wall in humans are lacking, but it is possible that fermentable carbohydrates exert similar trophic effect (Jahns et al., 2011).

Dietary fibers contribute to reduce transit time in the large intestine by exerting a bulk effect directly or indirectly by the increase of bacterial mass (Luria, 1960). In fact, there is a direct relationship between an accelerated transit time, an enhanced fecal bacterial mass and fecal N excretion (Stephen et al., 1987). Furthermore, we have shown that the increase in fecal N excretion was compensated for by a decrease in urinary urea (Younes et al., 1995a,b, 1996a, 1997). The laxative effects of fermentable carbohydrate are particularly interesting to prevent and to treat the constipation (frequent in patients with CRF) (Burkitt et al., 1974; Eastwood, 1983; Turnbull et al., 1986).

3. Relationship between fermentable carbohydrate intake and enterohepatic cycling of urea and ammonia

How do these changes in bacterial mass and stool bulk affect N metabolism? Fermentation, by stimulating microbial growth, increases the N requirements of microorganisms. Nitrogen reaching the colon is mainly of endogenous origin, protein coming from the small intestine, or urea coming either directly from the blood or from the small intestine. Indeed, with diets which provide a small quantity of fermentable carbohydrates, only small amount of undigested dietary proteins and endogenous proteins (pancreatic enzymes and sloughed mucosal cells) reach the large intestine. Here, they will be hydrolyzed and used for the microbial proliferation in the large bowel, but many of the end-products of protein fermentation are undesirable. However, when the intake of fermentable carbohydrates increases, N transfer may be not enough to promote an optimal bacterial growth. In such conditions, several investigations (Demigné & Rémésy, 1979; Langran, 1992; Younes et al., 1995a, 1995b, 1996a, 1997; Geboes et al., 2006) have shown that the blood urea constitutes the largest and the most available source of N for bacterial protein synthesis. As a result, fecal N excretion is significantly increased by comparison with fiber-free diets. (Younes et al., 1995a, 1995b, 1996a, 1997; Geboes et al., 2006; Wutzke, 2010)

In the 1980s, several hypothesis have been put forward for the manner in which fermentable carbohydrates brings about this effect : (i) the fecal N could originate from structural proteins of plant cell wall (Saunders & Betschart, 1980), and (ii) the fiber could decrease the digestibility of dietary protein in small intestine (Bender et al., 1979; Schneeman & Gallaher, 1986). Although these N sources may be significant, another source of fecal N is bacterial proliferation (Stephen, 1987). Bacteria make up ~ 55% of dry stool weight in humans on a western diet (Stephen & Cummings, 1980), and because bacteria are composed of 7-8% of N (dry weight) (Stephen, 1987), any increase in their colonic proliferation will increase fecal mass and N excretion.

Urea disposal in the large intestine has been shown in various species including humans (Demigné & Rémésy, 1979; Viallard, 1984; Forsythe & Parker, 1985; Moran & Jackson, 1990; Langran et al., 1992). In humans, it has been estimated that the urea hydrolyzed in the large intestine could represent approximately one-third of total urea produced by the liver (Richards, 1972). Various factors control the urea hydrolysis: the rate of urea transfer to the site(s) of hydrolysis, the activity of the bacterial urease, the demand of ammonia for the bacterial protein synthesis, and the availability of other N sources (Langran et al., 1992). However, some studies suggest that the human colon, unlike the colon of many animals, is relatively impermeable to urea and at most, a passive flux might allows diffusion of about 20% of the amount of urea destroyed (Bown et al., 1975; Moran & Jackson, 1990). But, these studies have entailed preliminary cleansing of the colon; yet removal of digestive constituents (bacterial urease, SCFA, carbon dioxide) is known to affect gastrointestinal permeability to urea (Dobbins & Binder, 1979; Kennedy & Milligan, 1980). Another study has shown, by direct measurements of the contribution of endogenous urea to fecal ammonia, that urea is a relatively minor source (8%) of fecal ammonia in healthy subjects with intact renal function (Wrong et al., 1985). The intensity of urea contribution to colonic ammonia is certainly dependent on the fermentable carbohydrate availability for maintaining highly active urease activity. Indeed, the transfer of urea is proportional to the concentration gradient of urea across the colonic wall; this explains the stimulatory effect of colonic bacteria via their ureolytic activity to promote urea uptake by the colon.

Consequently, in the presence of fermentable carbohydrates (particularly oligosaccharides which exerts osmotic effects and favors the ureolytic activity) and in case of hyperuremia, this transfer into the colon may become considerable (Fig.2A) (Younes et al., 2001). Some urea could be utilized in the distal ileum which presents a high permeability for this molecule (Gibson et al., 1976). However, the bacterial population in the terminal ileum is only one thousandth or so of that in the colon. Although the permeability of human ileum to urea is higher than that of the colon, the transfer of urea to the colon may be substantial because the transit time in the colon is longer.

Fig. 2. Effects of dietary conditions on cecal nitrogen flux in control (C) or uremic (U) rats fed fiber-free (FF) or fructooligosaccharide (FOS) diets. * Significant difference ($P<0.05$) between groups of rats fed FF diets and groups of rats fed FOS diets. † Significant difference ($P<0.05$) between groups of control rats and uremic rats. § Significant difference ($P<0.05$) between groups of rats fed the moderately low protein level and those fed the moderately high protein level.

A part of ammonia produced from urea will be used for bacterial protein synthesis which will be eliminated in the stool, and therefore fecal N excretion is increased (Younes et al., 1995; Bliss et al., 1996; Younes et al., 1997). Another part of ammonia will be absorbed and converted in the liver to urea or recycled by different ways for non-essential AAs synthesis such as glutamate and glutamine (Rémésy et al., 1997). Moreover, some AAs coming from bacterial metabolism could be recovered by the host, but the importance of this way is still poorly documented (Jackson, 1995, Aufreiter et al., 2011). In fact, the incorporation of ammonia into bacterial protein mainly leads to an irreversible loss of N via the fecal route and it is more significant when the quantity of fermentable carbohydrates is high. Our results support the view that there is a close relationship between the net flux of urea N towards large intestine and fecal N excretion, hence a lowering of plasma urea (Fig. 3) (Younes et al., 2001). A high rate of urea transfer into the cecum is favored by an enlarged surface area of exchange between blood and the luminal fluid and by an accelerated blood flow in the cecum (Rémésy & Demigné, 1989; Younes et al., 1997). All these parameters are enhanced by feeding various fermentable carbohydrates. In turn, a high supply of urea elevates the cecal pool of ammonia and elicits a substantial absorption of ammonia in spite of a marked acidification of cecal contents (Fig. 2B) (Younes et al., 2001). In fact, ammonia and SCFAs are generally considered to be transported across biological membranes as uncharged molecules (Bödeker et al., 1992). In colonocytes (intracellular pH 7.0-7.1) SCFAs and ammonia will be dissociated again, and it is conceivable that protons required for NH_4^+ formation arise from SCFA dissociation.

Fig. 3. Effects of dietary conditions on plasma urea concentration in control (C) or uremic (U) rats fed fiber-free (FF) or fructooligosaccharide (FOS) diets. * Significant difference ($P<0.05$) between groups of rats fed FF diets and groups of rats fed FOS diets. † Significant difference ($P<0.05$) between groups of control rats and uremic rats. § Significant difference ($P<0.05$) between groups of rats fed the moderately low protein level and those fed the moderately high protein level.

Thus, the enterohepatic cycle of urea and ammonia N observed in numerous works, (Stephen & Cummings, 1980; Forsythe & Parker, 1985; Rémésy & Demigné, 1989; Moran & Jackson, 1990; Jackson, 1995) and as represented in Fig 4, suggests that this process is not necessarily a futile cycle. It participates in both the elimination of urea N by the fecal route and in the N salvage, particularly with a low protein diet enriched with fermentable carbohydrate.

Fig. 4. Impact of fermentable carbohydrate intake on N enterohepatic cycle.

4. Present dietary approach to treat the patient with chronic renal failure

Until now, researches and dietetic propositions for CRF patients were based on the nephroprotection concept, making an attempt to maintain a satisfactory nutritional state. In other words, the aim of these researches and dietetic propositions were to delay the progression of renal deterioration, reduce urea toxicity and limit muscle wasting. Numerous studies have reported a reduction of the renal failure progression with a low protein diet. In fact, a linkage between glomerular hyperperfusion, hyperfiltration, and structural changes was suggested in studies involving dietary protein restriction (Brenner, 1985; Levey et al., 1996a, 1996b; Fouque et al., 2011, Garneata L & Mircescu G, 2011).

The relationship between the dietary protein restriction and renal failure progression is known for a long time. Approximately 60 years ago, Addis speculated that the severity of CRF could be improved by reducing the dietary protein level (Addis, 1948). Since then, a considerable body of evidence has been accumulated suggesting the slowing or temporary halting of the progression of CRF. In fact, a large number of diets have been proposed and more or less widely used during the last decades. The overall strategy was to reduce N intake by selecting foods of vegetable origin and by supplementing this "basal diet" with small amounts of protein of high biological value to satisfy the requirement for essentials amino-acids (AAs). Another approach was to use a supplementation of essentials AAs or

keto acids (KAs) (Giovannetti, 1989; Lin, 2009), however, the use of these KAs was not particularly convincing (Klahr, 1994; Aparicio et al., 2009).

Studies in CRF patients (randomized trial or not) reported that starting a restriction of dietary protein and phosphate early in the course of CRF has a considerable influence on the rate of progression of this disease (Mitch, 1991; Levey et al., 1996a, 1996b; William & Maroni, 1998; Mackenzie & Brenner, 1998; Garneata & Mircescu, 2010; Kalista-Richards, 2011; Fouque et al., 2011a). In experimental models, dietary protein restriction reduces the load of N metabolism end-products for excretion, limits the adaptive changes in remnant nephrons, and slows the tendency to renal disease progression (Hostetter, 1986). Despite the unambiguous support from experimental studies, the conclusive results are often regarded as unconvincing and as they do not meet strict statistical rules (Gretz & Strauch, 1986; Garneata & Mircescu, 2010).

Other works carried on within MDRD study (The Modification of Diet in Renal Disease: a randomized and controlled trials), it appeared that the protein restriction gives only a slight benefit for the patients with a moderate renal failure (Mackenzie & Brunner, 1998). Moreover, when the renal failure was at an advanced stage, the protein restriction, even severe and supplemented with KAs, did not really reduce the progression of the disease (Klahr, 1994). In fact, there is an initial diet-induced decline in GFR followed by a long-term beneficial effects of dietary protein restriction (appeared after 4 months), with an improvement of functioning nephrons conservation (Mackenzie & Brunner, 1998). This initial rapid reduction in GFR, accompanied by a reduction in protein excretion rates, is a functional effect and does not reflect a further loss of nephrons (Levey et al., 1996c). In second MDRD study, the authors concluded that the addition of KAs did not exert a beneficial effects (Klahr et al., 1994), and that for patients with a low GFR ($< 25 \text{ mL/min/1.73 m}^2$), a dietary protein intake of 0.6 g/kg/day should be prescribed (Levey et al., 1996a).

The question arises therefore on to the degree of the protein restriction. For health maintenance, a minimum daily supplies in protein was defined by the FAO in the range of 0.5 g/kg/day (FAO/WHO/UNU, 1985). In practice, in patients who are pre-dialysis and treated by a maintenance method, a protein supply lower than 0.6 g/kg/day has been proposed in association with KAs supplementation (El Nahas & Coles, 1986). However, the risk of protein malnutrition, and the constraints inherent to this supplementation led to recommend a moderate dietary protein supply of about 0.8 g/kg/day (Klahr et al., 1994; Tom et al., 1995; Levey et al., 1996a; Dumler, 2011; Fouque et al., 2011a).

In dialysis patients, the protein restriction question is more complex because there is a aggravated risk of protein-caloric undernutrition with an increased morbidity and mortality (30% of the dialysis patients) (Parker et al., 1983; Young et al., 1991). This leads to a rejection of protein restriction with, as a result, a proposed supply in the $1 \text{ to } 1.2 \text{ g/kg/day}$ range (Bergström, 1995; Cianciaruso et al., 1995; Qureshi et al., 1998; Antunes et al., 2010). However, it is still uncertain whether this policy is enough in order to equilibrate the N balance in these patients since there is a proportional relationship between the protein supply and the rate of N catabolism as it is estimated by the PCR (protein catabolism rate) (Movilli et al., 1993; Harty et al., 1994; Fouque et al., 2011a).

The protein-caloric undernutrition observed in dialysis patients is often linked to a deficient supply (Ikizler et al., 1995; Pollock et al., 1997; Kalantar-Zadeh, 2003), which is itself often linked to a depressed appetite (Bergström, 1995; Van Der Eijk & Farinelli, 1997). Moreover, seances of dialysis constitute in itself protein catabolism stimulation by means of an inflammatory response in contact with the membrane which induces the secretion of

hypercatabolic factors like interleukins (Valderrabano et al., 1996). The loss in glucose (25 g/seance) and in AAs (10-12 g/seance) can also decrease the protein anabolism capacity and thus led to an increased net proteolysis (Gutierrez et al., 1994; Ikizler et al., 1994). In practice, and in certain important undernutrition situations, it is necessary to provide a nutritional complement, especially AAs which are injected intravenously during the seance of dialysis. The dialysis fluid can be used also as a nutritional vehicle for supplementation of N (Chazot et al., 1997). The pre-dialytic parenteral nutrition seems to yield good results in order to preserve nutritional status (Cano et al., 1990), and it sounds to improve both morbidity and mortality on retrospective data (Capelli et al., 1994; Chertow et al., 1994).

Others studies showed that the catabolism rate of AAs and net protein synthesis could be affected by the speed of protein digestion (Boirie et al., 1997; Koopman et al., 2009). Thus, soluble proteins of milk are more quickly oxidized and lead to a less efficiency protein synthesis than casein. It is more helpful to have slowly digested carbohydrate than rapid carbohydrate, and in the same view, it also would be helpful to select slowly degraded proteins (in particular plant proteins). This approach has not been sufficiently investigated in comparison with the quantitative approach.

In the elderly, the development of renal diseases is frequently linked to pathologies as diabete and/or cardiovascular diseases (Attman & Alaupovic, 1990; Parillo et al., 1988; Blicklé et al., 2007; Ng et al., 2011). Consequently, it is important to control the supply of both carbohydrates and lipids. In this view, it has been shown that diets enriched in fiber can improve blood glucose control and reduce serum cholesterol levels in diabetic patients. It has been also shown that the preservation of remaining nephron in nephrectomized rats is tightly dependent on the nature of the carbohydrate ingested. The kidney preservation could be, thus, improved by the supply of complex carbohydrates rather than simple carbohydrates (Lakshmanan et al., 1983; Kleinknecht et al., 1986).

Control of lipid supply and the balance in fatty acids is also important since CRF patients are frequently hyperlipidemic with an increase of the total amount of plasma cholesterol, triglycerides, phospholipides, LDL and VLDL and a decrease in HDL (Attman & Alaupovic, 1990; Gentile et al., 1995; Axelsson, 2010; Ng et al., 2011). In some animal models with a CRF, it has been shown that low-fat diets have protective effects on the progression of glomerular damages (Kher et al., 1985; Diamond & Karnovsky, 1987; D'Amico et al., 1992; Brown et al., 2000).

Furthermore, it is well known that diets for the CRF patients must be restricted in phosphorus and potassium and provide a calcium supplementation in order to help the fecal elimination of the phosphate (Gin & Rigalleau, 1995; Fouque et al., 2011b). Because of nutritional constraints inherent to the renal deficiency, it is particularly important to maintain the energetic balance of the patients and to provide a nutrition rich in protective factors, in particular, antioxidants to limit the severity of oxidative stress.

5. Role of fermentable carbohydrate in the dietetic of chronic renal failure: Experimental bases and discussion

There are synergistic actions between high fermentable carbohydrate diets and low protein diets, particularly as to their plasma urea lowering effects, and, hence progression of CRF. Although the primary determinant of the plasma urea concentration is the dietary protein level, feeding fermentable carbohydrate has also an important effect on this parameter (Younes et al., 1995a,b, 1996a, 1997; Bliss et al., 1996). Consequently, it is interesting to

promote low protein diets, rich in various unavailable carbohydrates. This can be obtained by consuming a diet rich in plant products (cereal products, leguminous, vegetables and fruits). However, these diets are also particularly rich in potassium. Thus, to deal with this drawback, it is necessary to select foods rich in fermentable carbohydrate (resistant starch and oligosaccharides) to restrict the potassium supply.

Extra-renal urea excretion via the enteral route may be clinically relevant in patients with an impaired renal function. In CRF patients, the question of efficiency of the dietary protein restriction has seldom been considered according to the availability of fermentable carbohydrates. Consequently, it is necessary to carry out experiments in order to confirm these hypotheses and to determinate the optimal fermentable carbohydrate and protein supply for the protection of the renal function.

The selection of diets rich in slowly digested carbohydrates is particularly important in order to reduce the N catabolism because a part of AAs is metabolized for glucose production if the supply of carbohydrates is not optimal. In dialysis patients, catabolism is accelerated which theoretically increases the N demand. However, any increase of dietary N is expected to rise in parallel N catabolism and consequently precludes any significant improvement of the N balance. For this reason, it is important to increase the supply of the slowly digested carbohydrates in the diet of these patients which can contribute to decrease the hepatic gluconeogenesis from AAs. Therefore, in dialysis patients, it should be important that the fermentable carbohydrate would be provided together with a substantial decrease of the protein level in the diet. This is possible because the increase of complex carbohydrate led to a better utilization of dietary N. It would also be important, in future, to explore the interest of slowly digested proteins.

The efficiency of fermentable carbohydrates to reinforce urea-lowering of a low-protein diet has been illustrated by experimental works in the rat (Younes et al., 1995b, 1996a, 1998, 2001). It appeared possible, using a diet rich in fermentable carbohydrates and low in protein, to drastically reduce the concentration of plasma urea, down to 0.75 mmol/L (Younes et al., 1996a). This urea lowering-effect of fermentable carbohydrates has been also observed in rat models of experimental renal failure (Younes et al., 1997, 1998, 2001) and in patients with CRF (Rampton et al., 1984; Bliss et al. 1996; Younes et al., 2006).

In nephrectomized rats, we have shown that feeding fermentable carbohydrates decreased the concentration of plasma urea from 32 mg/dL to 22 mg/dL, a 30% decrease. When, in addition, the dietary protein level was reduced from 18% to 10%, plasma urea was decreased from 56 mg/L to 22 mg/dL, a 60% decrease (Younes et al., 2001) (Fig. 3). Moreover, our results obtained in nephrectomized rats showed that the fermentable carbohydrates were all the more efficient to shift N excretion from the urinary route towards the fecal route because the protein level was low. Thus, we have shown that with a 18% protein level, fecal N represented 22% of total N excretion in rats fed fermentable carbohydrate diet vs. only 13% in rats in fiber-free conditions; whereas, with a lower protein level (10% casein diet) fecal N represented 40% of total N excretion (Fig. 5C) (Younes et al., 2001). As a result of this increase in fecal N excretion, the net effect of feeding fermentable carbohydrates with a dietary protein restriction was to decrease urinary N excretion from approximately 270 mg/day (18% casein, fiber-free diet) to approximately 100 mg/day (10% casein, fermentable carbohydrate diet); this represents a 63% decrease of urinary N (Fig. 5B) (Younes et al., 2001).

We have also compared the effects of fermentable carbohydrate intake in normal and nephrectomized rats: the data indicates that the hypertrophy of the remaining kidney (+40-50%) was effective in ensuring a relatively high rate of urea excretion, but it was not

Fig. 5. Effects of dietary conditions on fecal and urinary N excretions and fecal percentage of total N excretion in control (C) or uremic (U) rats fed fiber-free (FF) or fructooligosaccharide (FOS) diets. * Significant difference ($P<0.05$) between groups of rats fed FF diets and groups of rats fed FOS diets. † Significant difference ($P<0.05$) between groups of control rats and uremic rats. § Significant difference ($P<0.05$) between groups of rats fed the moderately low protein level and those fed the moderately high protein level.

sufficient to counteract increased blood urea levels. Elevated blood urea had a minute influence on urea cycling and ammonia absorption in large intestine in rats fed the fiber-free diet. In contrast, a large increase in N fluxes through the large intestine was observed in nephrectomized rats fed fermentable carbohydrates (Fig. 2A,B). In these animals, a large part of urea taken up was reabsorbed as ammonia. This accelerated transfer of N in the large

intestine results in a slightly higher fecal excretion in nephrectomized rats, when compared to normal rats (Fig. 5A). In turn, this led to a significant decrease of plasma urea, less pronounced in nephrectomized rats fed fermentable carbohydrate diet (-30%) than in normal rats (-45%) (Fig. 3). The urinary N excretion was also more effectively lowered by fermentable carbohydrates in normal rats (-30%) than in nephrectomized rats (-20%) (Fig 5B) (Younes et al., 2001).

Fig. 6. Effects of dietary conditions on stool and urinary N excretions and the total N excretion in chronic renal failure patients consoming a fermentable carbohydrates (FC)-free diet or an enriched-FC diet. * Significat difference ($P < 0.05$).

The question which arises is to know if the fermentable carbohydrates have the same effects on N metabolism in healthy men as in those with CRF. To our knowledge, this point has not been well documented. In CRF patients, supplementation with gum arabic or ispaghula (hemicellulose) has been shown to reduce serum urea N levels by 12% and 19%, respectively (Rampton et al., 1984; Bliss et al. 1996). In parallel, the total fecal N excretion, and particularly the bacteria fraction, was significantly increased with fermentable carbohydrates and accounted for 59% of the total increase in stool N contents (Stephen et al., 1995; Bliss et al., 1996). This suggests that the large intestine can partially compensate for the renal failure, provided that an appropriate supply of fermentable carbohydrate and protein is allowed. More recently, in a prospective study (Younes et al., 2006), the impact of fermentable carbohydrates (40 g/day) on uremia and N excretion ways was investigated during five weeks in CRF patients in presence of a controlled protein diet (0.8 g/kg/day). Patients were their own controls and treated by crossing over method after randomization (5 weeks with fermentable carbohydrates vs 5 weeks without fermentable carbohydrates). Feeding fermentable carbohydrates significantly increased the quantity of N excreted in stools from 2.1 ± 0.8 to 3.2 ± 1.1 g/day ($P < 0.01$) and decreased, in parallel, the urinary N excretion from 9.4 ± 1.7 to 8.3 ± 1.4 g/day ($P < 0.01$). The total N quantities excreted by the two ways were unchanged by the fermentable carbohydrates, which showed that the FC was efficient to shift N excretion from the urinary route toward the digestive route (Fig. 6).

In consequence to this increase of urea transfer into the colon, the plasma urea concentration was significantly decreased from 26.1 ± 8.7 to 20.2 ± 8.2 mmol/L ($P < 0.05$). In this short trial, we have not shown a significant difference in the concentration of plasma creatinine, nor in the creatinine clearance. Any changes in the nutritional status parameters (albumin, prealbumin) have been noted. However, the body weight was significantly increased (+ 600 g) when the diet of patients was enriched in fermentable carbohydrates.

6. Conclusion

In CRF, the plasma concentration of the end-products of protein catabolism, especially urea, is increased. Although most of the dietary attempts to treat this disease and to decrease the serum urea N involve a reduction of N intake, an additional manipulation of diet would be to add fermentable carbohydrates, which can increase N excretion in the feces. Our works and those of others have shown that a low protein diet remains beneficial and the combination of these two dietary changes brings about the greatest fecal urea excretion, together with a reduced urinary excretion. Of course, the colon could not substitute completely itself to the renal function. Reciprocally, when the digestive elimination route is disturbed, the consequences of renal failure are amplified.

In practice, it is recommended to increase fiber gradually by using a large variety of vegetal products to provide 35-40 g of fiber daily (24 g from cereals products, leguminous seeds, and other starchy foods; 8 g from vegetables; 2-4 g from fruits; 4 g from resistant starches, oligosaccharides and various hydrocolloids). Nevertheless, because intolerance seems to exist toward certain food, it is necessary to ensure that the recommended products are well tolerated by considering the supply of potassium, which is particularly present in fruits. Because of social and family environments, it is difficult to change dietary habits; thus, it is sometimes necessary to recommend preparations enriched with fermentable carbohydrates. Finally, it is also important to indicate that a food rich in complex plant products could help facilitate the elimination of cholesterol and, hence, prevent the vascular complications caused by CRF. Moreover, plant products are rich in antioxidant micronutrients are very important in order to prevent lipid peroxidation and the production of free radicals, which is exaggerated in the CRF patients.

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Phone: +86-21-62489820
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