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Physiological Effects of Dietary Complex Carbohydrates and its Metabolites Role in Certain Diseases

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Abstract: Carbohydrate is one of the basic and an important food nutrient consumed worldwide. Like-wise Pakistani foods contain more carbohydrates than any other food nutrient consumed. Sometimes, Pakistani foods are devoid of protein and may contain only carbohydrates and fats as the major nutrients of the diet e.g. eating chapati (wheat bread) with potato curry. Certain non-communicable diseases can be avoided with adoption of proper healthier food habits and eating foods according to the needs of the body. These diseases are obesity, coronary heart disease, colonic cancer and gastrointestinal disorders (diverticular disease, constipation, hiatal hernia and hemorrhoids). Therefore complex carbohydrate should be an important constituent of our daily meal and it can be adopted for the management of certain diseases provided that it is used in proper amounts. Consumption of certain complex carbohydrates is associated with lower body weight, reduced blood cholesterol, reduced blood glucose and an increased crypt cell proliferation. Therefore, it is necessary and utmost important to know the various types of carbohydrates to enable us to decide to include carbohydrates in our daily food according to our health requirements. Not necessarily all the community need to know but at least those who are associated with nutrition and health management must know the beneficial as well as the harmful effects of carbohydrates.

Key Words: Complex carbohydrates, fibres, digestion, absorption, metabolites short chain fatty acids, diseases

Introduction

What are the complex carbohydrates ?: Complex carbohydrates refers to large molecular forms of carbohydrates (resistant starch and dietary fibres); are types of carbohydrates, which are not digested in the upper gastrointestinal tract and are fermented, in the large bowel by the action of various bacteria. The fermentation products are mainly short chain fatty acids (SCFAs) or volatile fatty acids (VFAs), methane (CH₄), hydrogen (H₂) and carbon dioxide (CO₂). The SCFAs produced from the fermentation are absorbed at site of production and transported to the liver via entero-hepatic circulation. The SCFAs play an important nutritional role that is discussed in the proceeding sections.

History and Definition of Complex Carbohydrates: In 1923 Kellogg and others stimulated the study of dietary fibre in the U.S.A. (Kellogg, 1923); however the term "unavailable carbohydrate" was used long before (McCance and Lawrence, 1929). The unavailable carbohydrate was later called "dietary fibre" (Hipsley, 1953) which was defined as "that portion of plant food resistant to hydrolysis by the alimentary enzymes of man" (Trowell, 1976). Kritchevsky (1988) defined as dietary fibres "plant material that resists digestion by human alimentary enzymes". It includes many different substances; with the exception of lignin, all are carbohydrate in nature. Chemically fibre was defined as "non starch polysaccharides (NSP)" (Cummings, 1981). The NSP include cellulose and non-cellulosic polysaccharides (NCP) (Kay, 1982). The latter includes pectin and hemicelluloses (structural polysaccharides); fructans, glucofructans, mannans and galactomannan (storage polysaccharides); gums and mucilages (isolated polysaccharides) containing a mixture of pentoses, hexoses and uranic acids (Kay, 1982) Apart from these lignin, protein, cuticular lipids and inorganic constituents, such as silica, magnesium, calcium and potassium are associated with the plant cell wall polysaccharides (Cummings, 1981). There is substantial evidence that some starch resists digestion in the upper gastrointestinal tract (GIT) and can act as a potential source of substrate for fermentation in the large bowel (Cummings and Englyst, 1987). This starch is known as resistant starch (RS) (Cummings and Englyst, 1987) and has been recently redefined

as "the sum of starch and products of starch degradation not absorbed in the small intestine of healthy individuals". Due to various chemical substances which could contribute to dietary fibre early definitions were inappropriate and the British Nutrition Foundation's Task Force introduced a new term "Complex carbohydrates" which includes both NSP and starches (British Nutrition Foundation's Task Force, 1990). In the UK, the term dietary fibre has been replaced in nutrition labeling by nonstarch polysaccharides (British Nutrition Foundation's Task Force, 1990 and Prosky, 2000).

Types of Complex Carbohydrates: Generally, complex carbohydrates are grouped into two major types; i) soluble complex carbohydrates and ii) insoluble complex carbohydrates. The soluble complex carbohydrates are soluble in water, viscous in nature and nearly hundred percent fermentable in large bowel whereas the insoluble complex carbohydrates are insoluble in water, non-viscous in nature and slowly fermentable in large bowel (Roberfroid, 1993). When these complex carbohydrates are eaten as a part of meal or fed to the experimental subjects behave differently and exhibit different physiological effects. For example, soluble complex carbohydrates may be helpful in the management of diabetes mellitus whereas the insoluble complex carbohydrates may be helpful in the management of constipation, diverticulitis, haemorrhoids and large bowel cancer (Gumaa *et al.*, 2001; Muir *et al.*, 1993). The classification based on its chemical nature is given in Table 1.

Complex Carbohydrates and Certain Diseases: Several diseases have very close link with complex carbohydrates. These diseases are cardiovascular diseases, ulcer, dental caries, constipation, appendicitis, obesity, varicose vein, colorectal cancer and diabetes mellitus. To understand the link between these diseases and complex carbohydrates it would be essential to know the process of digestion of the complex carbohydrates and their end products of digestion and metabolism.

Digestion of Complex Carbohydrates: Most starch is digested in the small intestine with glucose as the absorbed product but some

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Table 1: Major types of non-starch polysaccharides (NSP)

Primary Source	Major Group	Components Present	Summary of structures	Distribution in Foods
Structural Materials of Plant Cell Wall	Cellulose	-	Long-Chain β -Glucans	-
	Non-Cellulosic Polysaccharides	Pectic Substances	Galacturonans Aarabinoglectans	Mainly in Fruits and Vegetables
-	-	Hemicellulose	Arabinoxylan	Cereals
			Glucuron- Arabinoxylan	Fruits and Vegetables
			Glucuron-xylan	
			Xylo-glectans	
Non-Structural Polysaccharides	Gums Mucilages	-	β -Glucans	Cereals
			Wide Range of	Seed and Fruits
			Hetro-Polysaccharides	

British Nutrition Task Force, (1990)

Table 2: The principle substrates thought to be available for fermentation for large intestinal bacteria in a person consuming Western diets (Cummings and Macfarlane, 1991)

Substrate	Amount (g/d)
Non-starch polysaccharides	8-18
Resistant starch	8-40
Oligosaccharides	2-8
Unabsorbed sugars	2-10
Dietary protein	3-9
Pancreatic enzymes and other gut secretions	4-6
Mucus	2-3
Sloughed epithelial cells	Unknown

starch escapes digestion in the small intestine. All NSP escapes small intestine digestion because there is no mammalian enzyme capable of hydrolysing plant cell wall polysaccharides. Dietary NSP are not digested in the upper GIT but are extensively fermented by the bacteria to produce short chain fatty acids (SCFA) as major end products and some other metabolites. Acetate, propionate and butyrate are produced in the approximate molar ratio of 60: 25: 15 (Cummings and Englyst, 1987), but this can vary depending upon the nature of the carbohydrate being fermented (Weaver *et al.*, 1992).

Fermentation of Complex Carbohydrates: In the digestive tract of monogastric animals including man, micro-organisms ferment a wide range of endogenous and exogenous substrate (Table 2) to produce SCFA, methane, carbon dioxide and hydrogen in a manner similar to rumen fermentation (Cummings and Englyst, 1987). Fermentation of food is achieved by the concerted action of bacteria through anaerobic breakdown. Polymeric substrates are hydrolysed to their monomeric units, glucose, galactose, xylose, arabinose and uranic acids and then fermented via glycolysis to pyruvate and eventually to SCFA (mainly acetate, propionate and butyrate) together with some gases (Smith and Bryant, 1979; Wolin and Miller, 1983).

In rats, the molar ratio of the three major SCFA (acetate, propionate and butyrate) is greatly influenced by the diet. Key and Mathers (1993) observed a strong linear relationship between the amount of substrate (whole meal bread) supplied and the molar proportion of butyrate. Feeding purified NSP and RS (Tulung *et al.*, 1987; Walter *et al.*, 1988) or diets rich in NSP readily change the SCFA pattern in rats (Cheng *et al.*, 1987; Mathers, 1990; Goodlad and Mathers, 1990). Apart from the substrate, alteration in the bacterial population (Goodlad and Mathers, 1990), pH (Finlayson, 1986), bacterial growth rate (Sillely and Armstrong, 1984) and caecal transit time (TT)

(Mathers and Dawson, 1991) may affect the molar proportion of the SCFA. Changes in the pattern of branched chain SCFA are usually the net balance between production of these SCFA and their use for bacterial protein synthesis (Rasmussen *et al.*, 1988).

Absorption of Metabolites of Complex Carbohydrates: Short chain fatty acids are absorbed in the monogastric animals including man via passive diffusion in a manner similar to that observed for rumen epithelium (Levrat *et al.*, 1991; Fleming *et al.*, 1991). Alternatively, it has been proposed that SCFA may be absorbed via anionic exchange (Ruppin *et al.*, 1980; Argenzio and Southworth, 1977). Short chain fatty acids could be absorbed as un-dissociated acids (non-ionic diffusion), or sodium or potassium salts of short chain fatty acids (ionic diffusion) (Fleming *et al.*, 1991, Ruppin *et al.*, 1980; Argenzio and Southworth, 1977). The absorption has been shown to be accompanied by luminal increase in HCO_3^- and decrease in CO_2 , and by increased absorption of sodium, potassium and water. SCFA are most effectively transported at pHs lower than 7.0 and it has been proposed that in the human large intestine 60 % of SCFA are absorbed in the un-dissociated acid form (Ruppin *et al.*, 1980).

Energy contribution of SCFA in different species: Table 3 summarises estimates obtained in various species for the contribution of SCFA to the energy requirement of the whole body but this has been shown to vary with the type and amount of dietary intake. For example Ruppin *et al.* (1980) calculated that SCFA could supply 22 % of the energy requirements in human subjects whilst other estimates (Cummings, 1981; Grossklaus, 1983; McNeil, 1984) are much lower at 2-7 % based on 20 g of fibre fermentation daily.

Metabolism of SCFA: The SCFA are directly absorbed at the site of production and may be metabolised either locally in the gut, by the liver or by peripheral tissues. The SCFA absorbed may then be used for maintenance, growth and lipogenesis. The enzymatic activation of SCFA by formation of their respective acyl-CoA eg. acetyl-CoA, propionyl-CoA and butyryl-CoA are important factors regulating the rate of uptake of SCFA by different tissue (Bergman, 1990). Rat colonocytes have been shown to possess a butyryl-CoA synthetase which is more active than the acetyl-CoA and propionyl-CoA synthetases (Roediger, 1982). Most of the butyrate is usually oxidised to CO_2 and ketone bodies in pig (Imotso and Namiokka, 1978), rabbits, (Marty and Vemy, 1984), rats (Roediger, 1982) and humans (Roediger, 1982) by the colonic mucosa during its transportation to the bloodstream. Some of the propionate is also metabolised by the gut. The remaining butyrate, propionate and acetate are transported to the liver via

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Table 3: Estimates of contribution of SCFA produced in different sections of the digestive tract of various species to energy requirements of the whole body

Species	Organ	% of Energy requirements	Reference
Rat	Caecum	5	Yang <i>et al.</i> (1970).
Human	Large intestine	6-10	McNeil (1984).
Pig	Large intestine	11	Imotso and Namiokka (1978) and Kim <i>et al.</i> (1978).
Pig	Total hind gut	25	Rerat <i>et al.</i> (1987).
Rabbit	Caecum	12	Marty and Verny (1984).
Rabbit	Total hind gut	30	Marty and Verny (1984) and Parker (1976).
Pony	Caecum	30	Glinsky <i>et al.</i> (1976).

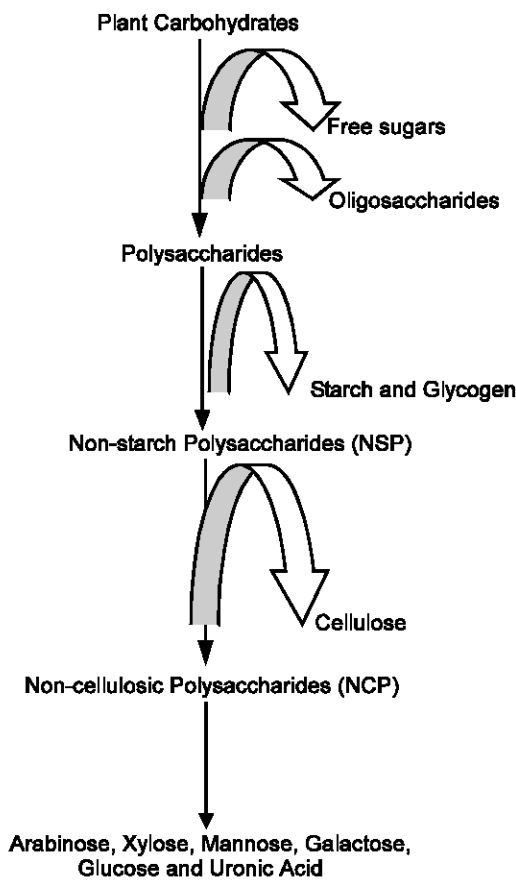


Fig. 1: Separation of plants carbohydrates

the portal vein (Bergman, 1990). The liver removes propionate and butyrate very efficiently and the uptake is close to 100 % whereas acetate uptake is generally limited in the liver. Goodlad and Mathers, (1990) observed very low concentrations of propionate and butyrate in peripheral blood and it has been observed that acetate comprises 90-98 % of the SCFA present in both arterial and peripheral blood (Bergman, 1990).

Metabolism of acetate: In ruminants only a small proportion of the absorbed acetate is utilized by the liver and acetyl-CoA synthetase activity is low in ruminant liver (Bergman, 1990). The acetate metabolism of monogastric animals varies from species to species. For example, lipogenesis occurs in humans and birds mainly in the liver whereas in ruminants and pigs lipogenesis occurs in adipose tissues (Bauman and Davis, 1975; Leaf, 1983;

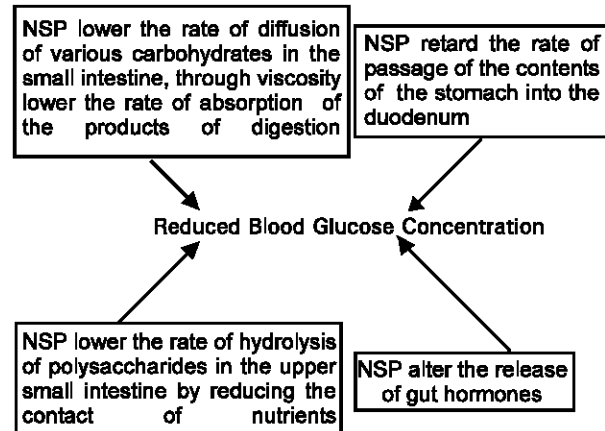


Fig. 2: Mechanism of action of NSP on blood cholesterol

Pearce, 1977). In rodents, lipogenesis occurs in both tissues. These differences in lipogenesis seem related to metabolism of acetate since acetyl-CoA can be easily incorporated into lipogenesis. In some studies it has been shown that hepatic acetate uptake is directly proportional to the concentration of acetate in the portal vein (Buckley and Williamson, 1977; Remesy *et al.*, 1980). In ruminants, acetate carbon is incorporated into fatty acids by both adipose tissue and the mammary gland more rapidly than is glucose carbon (Ballard *et al.*, 1969; Ballmain *et al.*, 1954; Vemon, 1981) whereas in rats glucose is the preferred substrate (Ballmain *et al.*, 1954). Acetate can be a significant source of fuel for skeletal muscles (Snoswell *et al.*, 1982). However, the quantitative importance and the metabolic fate of acetate in the simple stomach species such as humans and rats are not well understood.

Metabolism of propionate: Propionate is partially metabolized by the gut epithelium and liver takes up most of the remainder. Propionate is the only SCFA that can be a major source of glucose; acetate, butyrate and longer chain SCFA with an even number of carbon atoms cannot contribute to net synthesis of glucose. This is because these SCFA are converted to acetyl-CoA only and the acetyl-CoA enters the tricarboxylic acid (TCA) cycle. When acetyl-CoA enters the cycle two carbon atoms are lost as CO₂ and there is no net gain of oxaloacetate and, therefore, no net glucose synthesis is possible (Weinman *et al.*, 1957). The propionyl-CoA synthetase activity has been reported to be greater than acetyl-CoA synthetase activity (Ash and Baird, 1973 and Demigne *et al.*, 1986) as a result of which most of the absorbed propionate is removed by the liver (Goodlad and Mathers, 1990; 1991). Once propionate is absorbed, it can be used for gluconeogenesis or for energy production via the TCA cycle. In

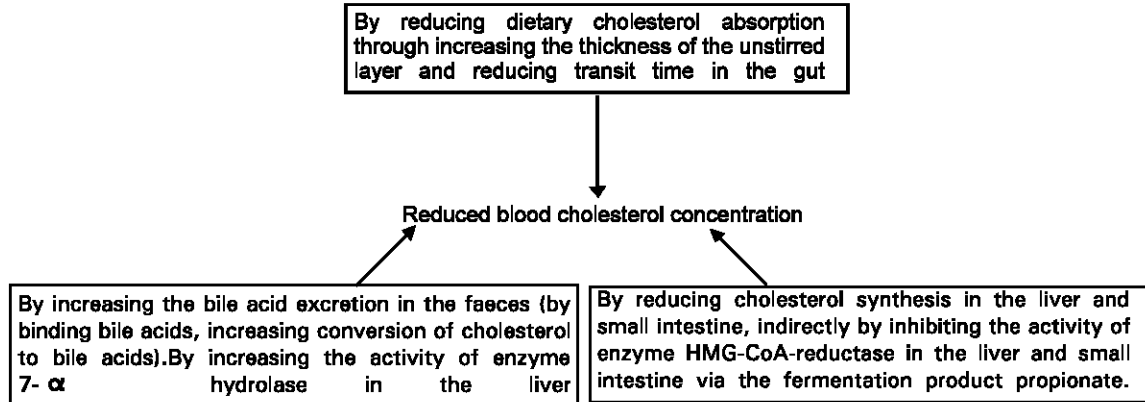


Fig. 3: Mechanism of action of NSP blood cholesterol

ruminants propionyl-CoA carboxylase activity has been shown to decrease during starvation; feeding feed rich in grain increases its activity and the amount of propionate absorbed (Baird and Young, 1975). Biotin and vitamin B₁₂ have been shown to be essential for the metabolism of propionate (Elliot, 1980). However, the net contribution of propionate to glucose production in simple-stomached animals is still not clear.

Metabolism of butyrate: Butyrate is metabolised by rumen and gut epithelium and by liver. Large amounts of butyrate are taken up by the gut epithelial tissue and by the liver. It has been suggested that only trace amounts can enter the post-hepatic bloodstream. The metabolic pathways of butyrate in ruminants and non-ruminants seem to be similar. Peripherally butyrate is utilised for the production of energy or used for lipogenesis and is removed for milk fat synthesis (Annisson *et al.*, 1963; Black *et al.*, 1961). Butyrate is readily oxidised by isolated rat hepatocytes (Roediger, 1982) and is an important source of energy for human colonocytes (Roediger, 1980). In liver, butyrate is converted to butyryl-CoA by an enzyme butyryl-CoA synthetase (Ash and Baird, 1973; Dougherty, 1984). Then it is rapidly converted to acetyl-CoA, longer chain fatty acids or to ketone bodies (Bergman and Kon, 1964; Katz and Bergman, 1969).

Effect of Complex Carbohydrates on Glucose Metabolism: The consumption of certain soluble NSP such as pectin and guar gum has been shown to lower postprandial blood glucose and insulin responses (Jenkins *et al.*, 1978) whereas the consumption of insoluble NSP such as wheat bran or cellulose are ineffective (Jenkins *et al.*, 1978). The mechanisms it involves are not established but proposed mechanisms of action of dietary NSP on blood glucose concentration are described in Fig. 2. Early studies using soluble viscous sources of NSP such as guar gum demonstrated that they could impair the glucose absorption (Jenkins *et al.*, 1977; Jenkins, 1983). In comparative studies it has been shown that the most viscous NSP seem to be the most effective; for example bran has little effect while guar gum produces the largest response (Edwards *et al.*, 1987; Jenkins *et al.*, 1978). The increased viscosity is probably involved in the reduced convective currents induced by the smooth muscle contractions (Blackburn *et al.*, 1984). Probably this action reduces the degree of mixing and thereby preventing the access of the nutrients in the luminal bulk phase to the absorptive epithelium. The rate of absorption is decreased and more food travels down the gut (Jenkins, 1983). It has been proposed that intestinal absorption of nutrients (final digestion products of SI) depends on

the thickness of the unstirred layer (unstirred diffusion barrier) overlaying the absorptive surface of the SI. Viscous soluble NSP have been shown to reduce the interaction between the nutrients and enzymes and the rate of absorption (Flourie *et al.*, 1984; Low, 1988). Guar gum has been reported to increase the viscosity of the gut contents (Johnson, 1990) and alter the mucosal enzymes activities (Elsenhans *et al.*, 1981). Mathers (1992) reported that guar gum feeding to rats had no effect on the maltase activity but sucrase activity was reduced in the proximal SI and the activity was increased in the distal ileum. The suggested mechanisms are presented in the Fig. 2.

Effect of Complex Carbohydrates on blood cholesterol: Feeding some NSP reduces blood cholesterol concentration in humans as well as in experimental animals (Gumaa *et al.*, 2001; Anderson *et al.*, 1991; Nishina *et al.*, 1991; Aro *et al.*, 1984; Mclvor *et al.*, 1986). Dietary NSP has been suggested as a natural and useful hypocholesterolaemic agent (Jenkins *et al.*, 1980). The effect on blood cholesterol depends on the type and quantity of dietary NSP eaten (Hundemer *et al.*, 1991; Leadbetter *et al.*, 1991; Lopez-Guisa *et al.*, 1988; Shinnick *et al.*, 1990; Hollenbeck *et al.*, 1986; Kestin *et al.*, 1990; Albrink *et al.*, 1979). The dietary NSP and some dietary fats can alter the hepatic LDL receptor activity (Norum, 1992; Topping *et al.*, 1990). The reduced blood cholesterol concentration usually involves a reduction in the low-density lipoprotein (LDL) cholesterol fractions whereas high-density lipoprotein (HDL) cholesterol is increased (Nishina *et al.*, 1991). This may be of particular importance in the light of the present evidence that the occurrence of CVD is strongly related to decreased HDL cholesterol concentration (Drexel *et al.*, 1992; Assmann and Schulte, 1992) and increased LDL cholesterol concentrations (Grundy, 1990). Work with experimental animals including rat, rabbit, chicken and swine have indicated that the supplementation of atherogenic diets with soluble NSP sources retards the progression of atherosclerosis whereas insoluble NSP do not have this effect (Kritchevsky, 1982; Kritchevsky, 1990). However, the exact mechanism of action is not clear and is open for further research.

Proposed mechanisms of actions of Complex Carbohydrates: The proposed mechanisms by which dietary NSP reduce blood cholesterol concentration include physical effects for example increased digest viscosity, enhanced bile acid excretion and altered digestion and absorption of lipids (Topping, 1991) as indicated in the Fig. 3.

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Reduced cholesterol synthesis: One of the leading hypotheses has been the inhibition of cholesterol synthesis in hepatocytes via the fermentation products SCFA (especially propionate) Illman *et al.*, 1988. Thacker *et al.* (1981) and Thacker and Bowland (1981); Boila *et al.*, (1981) reported that feeding 5 % propionic acid in the diet lowers blood cholesterol concentration in pig. It has also been reported that the addition of propionic acid at concentration of 15 and 30 mM to bovine liver homogenate inhibited HMG-CoA reductase activity (Bush and Milligan, 1971). These concentrations of propionate are very much higher than those found *in vivo* so the practical significance of these observations must be in question. With isolated rat hepatocytes propionic acid inhibits cholesterol and fatty acid synthesis using ¹⁴C-acetate, ³H₂O and ¹⁴C-mevalonate as tracer (Ide *et al.*, 1978). However, in human subjects, it has been shown that feeding sodium propionate at the rate of 7.5 g/d in a capsule form did not lower the serum total cholesterol but increased HDL cholesterol concentration (Venter *et al.*, 1990).

Complex Carbohydrates enhance faecal bile acids excretion:

The cholesterol lowering effect of dietary NSP could be predominantly because of the interruption of the bile acid circulation (enterohepatic cycle). Studies with dietary guar gum in rats have been shown that the activity of the enzyme 7 α -hydroxylase (EC 1.14.13.17) which is the rate limiting step in the conversion of cholesterol to bile acids in the liver is increased and at the same time there is increased faecal bile acid excretion (Ide *et al.*, 1990). It has been observed that other dietary NSP increase the 7 α -hydroxylase activity in the liver of rats and decrease the bile acid pool (Ide *et al.*, 1990; Marcus and Heaton, 1986; Arjmandi *et al.*, 1992; Turley *et al.*, 1991). In hyperlipidaemic subjects 40-50 g of pectin /d reduced blood cholesterol concentration; this decrease was associated with the increase cholesterol elimination of bile acids in the stool which is then balanced by enhanced cholesterol synthesis (Arjmandi *et al.*, 1992; Ebihara and Schneeman, 1989; Story, 1985). In this respect, soluble NSP act in similar way to the bile acid sequestrant such as cholestyramin but this effect is associated with the type of NSP fed to the experimental subjects (Turner *et al.*, 1990). Similar effects have been observed *in vitro* with different dietary NSP sources on bile acids (Story and Kritchevsky, 1976).

Viscosity and transit time: The ingestion of soluble NSP increases the viscosity of the contents of the stomach and small intestine and therefore might interfere with digestion and absorption of lipids (Topping *et al.*, 1988 and Blackburn and Johnson. 1981) in similar way to that described earlier.

Effect of NSP on Crypt Cell Proliferation (CCP): There is substantial evidence in the literature that soluble NSP sources increase epithelial cell proliferation in the gut (Pell *et al.*, 1992; Lupton *et al.*, 1988) but the mechanism for this effect is not established. There seems to be many different mechanisms involved simultaneously in increasing the intestinal CCP, such as the increased delivery of organic matter (OM) to the large bowel (Mathers *et al.*, 1993). The increased supply of OM to the large bowel stimulates bacterial fermentation resulting in increased SCFA production and a more acidic pH. Increased concentration of SCFA and reduced pH may be responsible for the elevated CCP (Lupton and Kurtz, 1993). Sakata (1987) reported that CCP was stimulated in the caecum and colon by butyrate injection into the caecum. Goodlad *et al.*, (1989) reported that dietary NSP sources increase the CCP in the small intestine and colon in conventional rats whereas CCP was not affected in germ-free animals and concluded that it is the fermentation product which

increase the cell proliferation. Another, mechanism by which the soluble NSP may influence intestinal cell growth is through the binding of luminal inorganic ions (James, 1980), such as calcium, which is considered to be important in the control of cell proliferation (Durham and Walton, 1982). Soluble NSP bind bile acids which have been shown to damage the mucosal cell surface causing higher rates of cell sloughing and resulting in compensatory stimulation of cell synthesis (Jacobs and Lupton, 1984). It has been shown that hormones play an important role in the regulation of epithelial cell proliferation and soluble NSP affect gut hormones such as entero-glucagon and gastrin (Pell *et al.*, 1992; Winsette *et al.*, 1986).

Conclusions: Consumption of certain complex carbohydrates is associated with lower body weight, reduced blood cholesterol, reduced blood glucose and an increased crypt cell proliferation. A possible mechanism of action is related to viscosity and gel forming abilities.

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