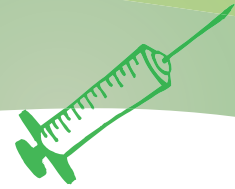


Astaxanthin and Type 2 Diabetes

Retards Glucose Toxicity and Kidney Damage



Draining the World Wealth



Diabetes mellitus is a worldwide epidemic that is critically linked to prevalence of obesity. More than 220 million people have diabetes and by the year 2030 the figures are expected to grow to 360 million. The diabetes is aggressively growing in both emerging and developed country.

According to WHO, the Asian continent has over 90 million people suffering from diabetes – India (40 million) China (29 million); Indonesia (13 million) and Japan (7 million). The prevalence of diabetic patients remains pervasive in USA (22 million), Brazil (6 million), Pakistan (8 million); Russia (6 million); Italy (5 million) and Turkey (4 million). Even in the African region over 10 million people suffer from diabetes, especially in Nigeria where it is expected to reach 5 million within the year 2030.

Diabetic complications lead to heart disease (approximately 65% of death amongst diabetics), blindness, kidney failure and amputations. As a result, the indirect and direct medical expenditure of diabetics represent almost 5 times that of a non-diabetic.

Type 2 Diabetes: A Preventable Disease

In most cases, diabetes is treated with medication, although about 20% of diabetics may be managed by lifestyle changes. This means that even if we cannot change the genetic influences, fortunately, for most of us diabetes is preventable; for example, making dietary changes, taking nutritional supplements and exercising. To highlight this, people in high risk groups who achieve a 5-7% cut in body weight will reduce risk of developing diabetes approximately 58% across all age and ethnic groups.



While the debate between the contributory effects of carbohydrate and fat intake continues unabated, research reveals a strong link between foods with high glycemic index and prevalence of type 2 diabetes. Excess blood glucose needs to be converted by insulin (produced by the

pancreas β -cells) into glycogen stores, however, when glycogen stores are full, glucose is converted into fat. Over time, the body's cells may eventually become desensitized to insulin making it necessary to produce more insulin to achieve the same affect. It is this process that would eventually lead to a state known as hyperinsulinaemic state. As a result, the body loses its ability to control high blood glucose levels (hyperglycemia) that could result in toxic conditions and promote further complications such as kidney failure.

New Evidences Emerging from Human Studies

In an anti-aging study conducted by Iwabayashi *et al.*, (2009), 20 female volunteers with increased oxidative stress burden ingested 12 mg/day of astaxanthin for 8 weeks. Results evidenced a significant decrease of diabetes-related parameters that collectively predict trends in diabetes development. Firstly, astaxanthin reduced cortisol by 23 percent ($p < 0.05$). High levels of cortisol decreases metabolism of glucose, which contributes to increased blood glucose and fat levels that eventually lead to insulin resistance. Secondly, astaxanthin reduced LDH by 6.5% percent ($p < 0.01$). Overexpression of LDH activity interferes with normal glucose metabolism and insulin secretion. Thirdly, astaxanthin decreased the glycated hemoglobin molecules HbA1c by 4% ($p < 0.01$) a direct indication of the level of glucose in the blood.

Astaxanthin Retards Glucose Toxicity and Kidney Damage

Astaxanthin displayed positive effects in a type 2 diabetic mouse model in that it reduced the disease progression by retarding glucose toxicity and kidney damage. This has profound implications for people who belong to high risk groups, display pre-diabetic conditions (impaired fasting glucose or impaired glucose tolerance) or want to manage advanced diabetic kidney problems (nephropathy).

Studies suggested that reactive oxygen species (ROS) induced by hyperglycemia contributes to the onset of Diabetes mellitus and its complications. Non-enzymatic glycosylation of proteins and mitochondria, prevalent in diabetic conditions, is a major source of ROS. For example, pancreatic β -cells kept in high glucose concentrations show presence of advanced glycosylation products, a source of ROS, which cause the following: i) reduction of insulin expression and ii) induction of cell death (apoptosis). β -cells are especially vulnerable to ROS because these cells are inherently low in antioxidant status and therefore, requires long term protection. A recent study demonstrated that antioxidants (N-acetyl-L-cysteine, vitamins C and E) exerted beneficial effects in diabetic conditions such as preservation of β -cell function, so it is likely that a more potent antioxidant such as astaxanthin can do the same or better.

In another study conducted by Preuss *et al.* (2009), 12 rats fed with 25mg/kg of astaxanthin show a significant decrease in insulin resistance by 13.5% ($p < 0.05$) and various anti-inflammatory markers that collectively correlate with diabetes development. Firstly, astaxanthin decreased interleukin-6 (IL-6) by 10.5 percent ($p < 0.01$). Diabetic patients have elevated blood levels of (IL-6), which is known to increase inflammation and the development of vascular disease and atherosclerosis. IL-6 has in addition to its immunoregulatory actions been proposed to affect glucose homeostasis and metabolism directly and indirectly. Secondly, astaxanthin decreased MCP-1 by 14% ($p < 0.05$). MCP correlates with parameters of renal function, glucose and lipid metabolism. MCP-1 can attract and activate macrophages and T cells from the circulation to the local kidney and ultimately injure the renal tissue. Thirdly, astaxanthin decreased TNF- α by 23% ($p < 0.05$), which play an important role in the insulin resistance of obesity and diabetes. Administration of TNF- α to animals can induce insulin resistance whereas inhibition of TNF- α can improve insulin sensitivity in animals.

Modulation of Glucose Toxicity

Uchiyama *et al.*, 2002 demonstrated in obese diabetes type 2 mouse model that astaxanthin preserved pancreatic β -cell dysfunction against oxidative damage. Treated mice received 1 mg astaxanthin/day at 6 weeks of age and then tests performed at 6, 12 and 18 weeks. Observations of astaxanthin treated mice (N=8) included: i) significantly reduced fasting glucose sugar levels at 12 ($P < 0.01$) and 18 weeks ($P < 0.01$); and ii) decreased glucose ($P < 0.001$) and insulin ($P < 0.001$) levels in the blood serum. In addition, treated rats displayed better response profiles to the intraperitoneal glucose tolerance test (IPGTT at 1g glucose/kg body weight, Figure 1 and Figure 2). This showed that astaxanthin preserved pancreas function and insulin sensitivity. Furthermore, preliminary renal damage assessment measuring urinary albumin levels revealed significantly lower glomerular (kidney) damage. This was confirmed in another study by Naito *et al.*, 2004, who looked at diabetic nephropathy in the type 2 diabetic mouse model (Figure 3). The authors postulated that astaxanthin can also circumvent high glucose toxicity which normally leads to increased oxidative stress and pathogenesis of kidney damage.

Figure 1. Astaxanthin improved the glucose levels in the Intraperitoneally Glucose Tolerance Test (IPGT) in diabetic mouse model (Uchiyama *et al.*, 2002)

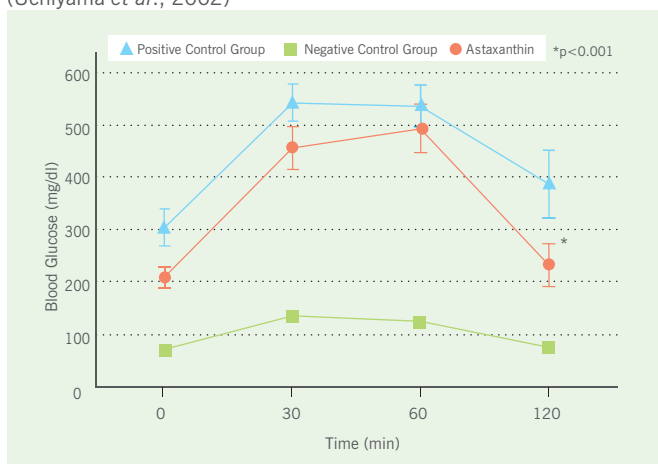


Figure 2. Astaxanthin preserved insulin sensitivity in the diabetic mouse model (Uchiyama *et al.*, 2002)

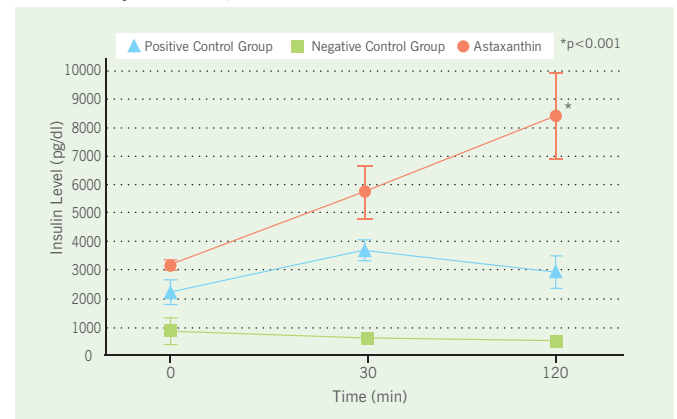
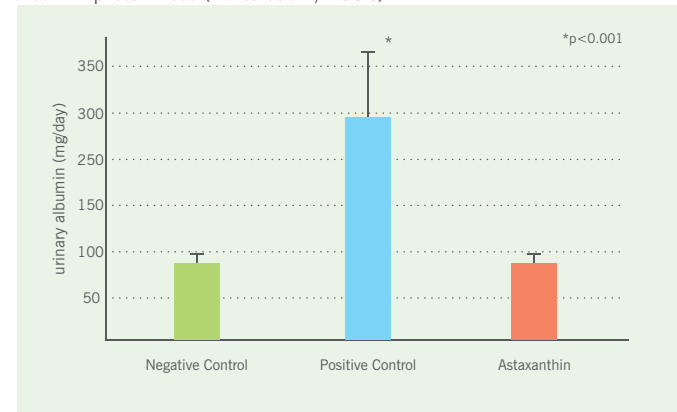


Figure 3. Astaxanthin protected kidney function measured by urinary albumin protein loss (Naito *et al.*, 2004)



Prevention of Diabetic Nephropathy

As well as substantiating observations by Uchiyama *et al.*, Naito demonstrated that astaxanthin treated type 2 diabetic mice which normally shows renal insufficiency at 16 weeks of age in fact exhibited 67% less urinary albumin loss (N=5, $P < 0.05$) and figure 4 shows 50% less DNA damage (8-OHdG, $P < 0.05$). Furthermore, the increased protein loss was due to the vascular size ratio increase of 250% in the diabetic model. In astaxanthin treated mice, this area was significantly ($P < 0.05$) reduced by almost 54% (Figure 5).

Figure 4. Astaxanthin reduced the amount of DNA damage indicated by urinary 8-OHdG levels (Naito *et al.*, 2004)

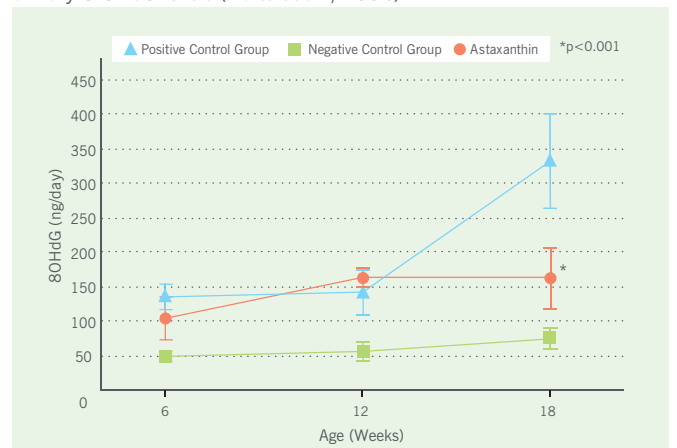
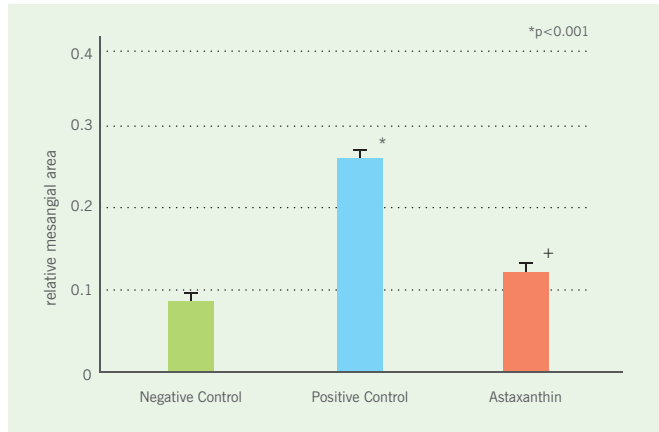


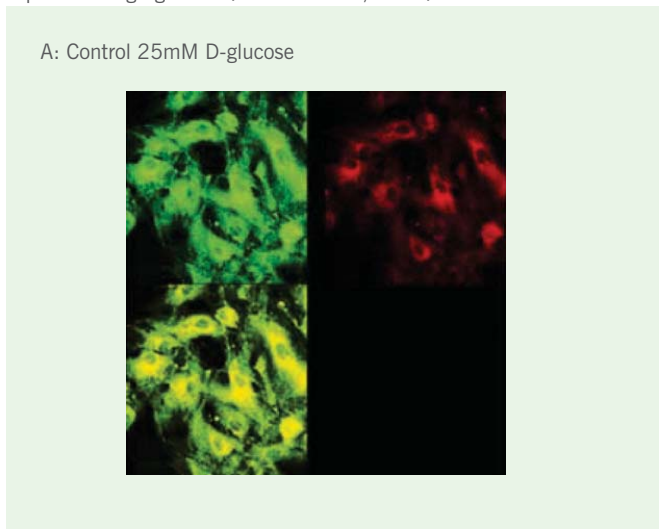
Figure 5. Astaxanthin preserved the relative mesangial area. + $p < 0.05$ vs positive control (Naito *et al.*, 2004)



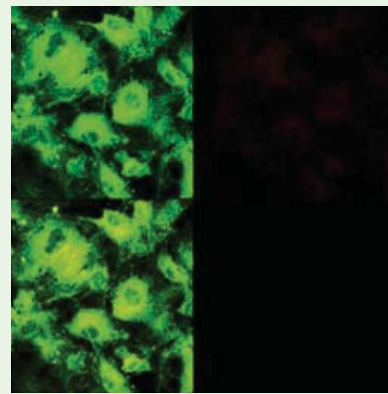
Earlier it was unclear how astaxanthin could ameliorate the progression of diabetic nephropathy, but new evidence revealed additional information in the mechanism of action. Naito *et al.*, (2006) examined changes in the gene expression profile of glomerular cells in diabetic mouse model during the early phase of diabetic nephropathy. The mitochondrial oxidative phosphorylation pathway was most significantly affected by high-glucose concentration (mediated via reactive oxygen species). Long term treatment with astaxanthin significantly modulated genes associated with oxidative phosphorylation, oxidative stress and the TGF- β -collagen synthesis system.

Manabe *et al.*, 2007 went further and analyzed normal human mesangial cells (NHMC) exposed to high glucose concentrations. In the presence of astaxanthin, it significantly suppressed ROS production (Figure 6) and inhibited nuclear translocation and activation of NF- κ B (Figure 7) in the mitochondria of NHMC. Furthermore, this was the first time to detect astaxanthin in the mitochondrial membrane (Table 1) and its presence also suppressed ROS attack on membrane proteins ($p < 0.05$).

Figure 6. Astaxanthin reduced ROS production in NHMC- mitochondria exposed to high glucose (Manabe *et al.*, 2007)



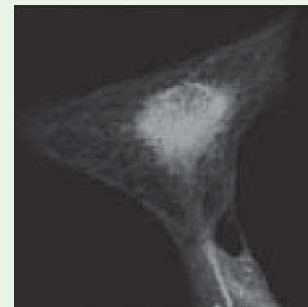
B: Astaxanthin + 25 mM D-glucose



Top left panel: mitochondria as green fluorescence, Top right panel: ROS as red fluorescence; Bottom right panel: Merged picture as yellow fluorescence.

Figure 7. Astaxanthin suppressed high-glucose induced nuclear translocation and activation of NF- κ B (Manabe *et al.*, 2007)

A: NHMC in 25 mM D-glucose



B: NHMC in 25 mM D-glucose and astaxanthin



Table 1. Astaxanthin content in NHMC mitochondria expressed as percentage of total astaxanthin added. Mean of 3 samples. (Manabe *et al.*, 2007)

	Astaxanthin content (% of added astaxanthin)	
	Mitochondria	Cytosol
Astaxanthin 10^{-6} M	0.33 ± 0.12	0
Astaxanthin 10^{-5} M	0.16 ± 0.05	0

Outlook

Although clinical trials involving antioxidants in humans have only recently begun, these preliminary results concluded that strong antioxidant supplementation may improve type 2 diabetic control and inhibit progressive renal damage by circumventing the effects of glycation-mediated ROS under hyperglycemic conditions. Astaxanthin improved pancreas function, insulin sensitivity, reduced kidney damage and glucose toxicity in diabetic mouse models. New techniques by gene chip analysis and fluorescence imaging revealed further details of mechanism and site of protection by astaxanthin. Further research and clinical studies are still required. However, it is reasonable to suggest that astaxanthin may be useful as part of a nutrigenomic strategy for type 2 diabetes and diabetic nephropathy.

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