POLISH JOURNAL OF FOOD AND NUTRITION SCIENCES

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Pol. J. Food Nutr. Sci.
2010, Vol. 60, No. 2, pp. 99-105

ROLE OF FAT AND THE *N*-3 POLYUNSATURATED FATTY ACID FAMILY IN THE PREVENTION AND TREATMENT OF DIABETES MELLITUS – A REVIEW

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Key words: *n*-3 polyunsaturated fatty acids, diabetes mellitus, dietary habits, molecular mechanism

Type 2 diabetes mellitus is a world wide problem, with obesity being a primary risk factor of this disease, mainly caused by poor diet and lack of physical activity. In the diet of subjects with diabetes, it is not only the quantity but also the quality of fat ingested that appears to be of great importance. Presented in this article is a review of the role of nutritional fat on insulin signaling and its risk involvement in diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a metabolic disease, characterised by hyperglycemia due to defects in insulin secretion, insulin action, or both [ADA, 2002]. Type 2 of diabetes is classified by The World Health Organization (WHO) as an non-communicable disease, which mainly arises due to an unhealthy diet and lack of physical activity [WHO, 2003b].

Recently compiled data show that approximately 150 million people have diabetes mellitus worldwide, and that this number may well double by the year 2025 [Kemper *at al*., 2004; Wild *et al.,* 2004]. Considering the fact that being overweight or obese pose a major risk for type 2 diabetes, it is important to reduce the prevalence of excess body fat mass [Avogaro, 2006; Boden, 2003; Doucet *et al*., 1998; Leonetti *et al*., 1996; Mostad *et al*., 2004; Proietto, 2005]. Unfortunately, the statistical analyses of obesity prevalence have revealed that obesity has reached epidemic proportions globally, with more than 1 billion adults being overweight – at least 300 million of these being clinically obese [WHO, 2000]. Given the increasing prevalence of obesity, it is likely that these figures provide an underestimate of future diabetes prevalence. Many developed countries are experiencing increasing numbers of overweight and obese adults and children, and closely linked increases in type 2 diabetes [WHO, 2003a].

Numerous studies underline fat intake as the main etiologic factor in the development of type 2 diabetes [Avogaro, 2006; Doucet *et al.,* 1998; Julius, 2003; McGarry, 2002; Oakes *et al*., 1997]. Both excess glucose and fat can cause insulin resistance in muscle and fat tissues, and excess fat also causes insulin resistance in the liver [Oakes *et al*., 1997; Oliver, 1997; Parillo *et al.,* 1992; Petersen & Shulman, 2002; Sethi *et al.,* 2002]. High fat intake and fat infusion rapidly lead to the development of insulin resistance, caused by impairment in glucose transport [Mayer-Davis *et al.,* 1997; Oakes *et al*., 1997]. Furthermore, the dietary influence of fat on the fatty acid composition of cell membranes, can affect membrane fluidity or insulin-mediated signal transduction and insulin action [Baur *et al.*, 1999; Hulbert *et al.,* 2005; Feskens & Dam, 1999]. A study by Clamp *et al.* [1997] has revealed that the saturated and monounsaturated fatty acid content of membranes is not as dependent on the dietary fatty acid intake, however, the polyunsaturated fatty acids (PUFA) content of muscle and fat tissue membranes, especially *n*-3/*n*-6 ratio appears to be of prime importance in the etiology of insulin resistance [Feskens *et al.,* 1995]. However, some studies have been inconclusive, indicating that the influence of total fat and fatty acids on diabetes mellitus development is overestimated [Long & Pekala, 1996; Zierath *et al*., 1997]. Possible roles played by fat and particularly essential fatty acids in the insulin-signaling pathway and risk of diabetes mellitus are discussed in a light of recent evidence.

FAT INTAKE AND THE RISK OF DIABETES MELLITUS

Dietary fat and its relation to obesity and diabetes mellitus has been a controversial issue for several years [Ascherio *et al.*, 1999; Bray *et al.*, 2002; Doucet *et al.*, 1998; Long & Pekala, 1996; McGarry, 2002; Proietto, 2005; Salmerón *et al*., 2001; Zierath *et al*., 1997]. It arises from the implication of dietary fat in the development of insulin resistance in both animals and humans [Chambrier *et al.,* 2002; Fickova *et al.,* 1998; Homko *et al*., 2003; Mayer-Davis *et al.,* 1997; Storlien *et al.,* 1991]. Although there are some genetic causes

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for insulin resistance, the most common cause is an excess of nutrition, a condition called „nutrient toxicity" [Oakes *et al*., 1997]. A high-fat diet clearly influences the prevalence of obesity and increases body fat content. All of these changes have been associated with altered glucose metabolism [McGarry, 2002; Proietto, 2005]. Positive associations have been reported with animal fat [Storlien *et al.,* 1991] and especially with the consumption of saturated fat [Summers *et al.,* 2002]. The cross-sectional IRAS (the Insulin Resistance Atherosclerosis Study) provided evidence that high intake of dietary fat worsened insulin sensitivity in the group of 1173 men and women with no history of diabetes [Mayer-Davis *et al.,* 1997]. The alarming finding was that unfavorable fat consumption was increased in subjects that had been newly diagnosed with type 2 diabetes. In a study from the Netherlands it was revealed that the total fat consumption was 40.9% of energy intake with saturated fatty acids consumption accounting for 15.0% of this intake [van de Laar *et al*., 2004]. Nevertheless the influence of dietary fat on the development of type 2 diabetes is uncertain. A prospective twelve year follow-up study of 1462 women found no significant associations between total dietary fat or specific types of fat with the risk of diabetes. However, the researchers did not adjust for the different types of fats ingested [Lundgren *et al*., 1989]. In a large prospective study of women in an age- and BMI-adjusted analyses, higher total fat intake was weakly correlated with a greater risk of developing diabetes [Salmerón *et al*., 2001]. The international multi-center cohort EPIC study (European Prospective Investigation of Cancer-Norfolk study) provided evidence that daily fat intake, as well as saturated fatty acids were not noticeably associated with the risk of type 2 diabetes [Trichopoulou *et al.*, 2005]. Another large prospective study of women also revealed no association between total fat intake and the risk of type 2 diabetes [Liu e*t al*., 2006].

The above mentioned studies indicate that it is probably the quality of fats consumed in the diet that is a risk factor for the development of type 2 diabetes and it is much more important then their quantity of fat [Ascherio *et al.,* 1999; Long & Pekala, 1996; Taouis *et al.,* 2002; Zierath *et al*., 1997]. This suggestion has been confirmed by the fact that in the United States, the intake of fat appears to be declining, whereas the prevalence of obesity is still rising – a state which is called the "American paradox" [Bray *et al.*, 2002; Heini & Weinsier, 1997]. Moreover, it is known that weight gain can be influenced by the intake of different kinds of fatty acids. Studies have demonstrated a significant positive correlation between the percent of dietary energy as total fat and body fatness in the group of adult males who were ingesting higher total fat as saturated and monounsaturated fatty acids which in turn was significantly associated with increased visceral adiposity. However, polyunsaturated fatty acid intake had no statistical effect on fatty tissue deposition [Harding *et al.,* 2004].

Not only is the quantity of fatty acid intake important in the development of obesity – the primary risk factor of type 2 diabetes, but dependant on the fatty acid involved there are various responses to inflammatory signals and insulin resistance [Bray *et al.*, 2002; Nettleton & Katz, 2005; Proietto, 2005]. In addition, it appears that different types of fat have different effects on insulin action. Saturated fats have been implicated in causing insulin resistance, whereas polyunsaturated, especially *n*-3 fatty acids largely do not appear to have adverse effects on insulin action [Harding *et al*., 2004; Salmerón *et al*., 2001; Sanders *et al.* 2006; WHO, 2003a]. However some studies have suggested that total fat and saturated and monounsaturated fatty acid intake are not associated with increased risk of developing type 2 diabetes, but only polyunsaturated fatty acids lead to a substantial reduction in risk of this disease [Salmerón *et al.*, 2001].

N-3 POLYUNSATURATED FATTY ACIDS IN DIABETIC DIET

Recent studies have reported a lower prevalence of impaired glucose tolerance and type 2 diabetes in populations consuming large amounts of *n*-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFA), these fatty acids are found mainly in fish [Delarue *et al.,* 2004; Ebbesson *et al.,* 2005; Nettleton & Katz, 2005; Summers *et al.,* 2002]. The *n*-3 LC-PUFA, mainly eicosapentaenoic acid (EPA, C 20:5 n-3) and docosahexaenoic acid (DHA, C 22:6 n-3), cannot be synthesized by humans and therefore it is vital that they are derived from dietary sources, mainly marine products and fish oil products [Gibney *et al.,* 2005].

Dietary *n*-3 polyunsaturated fatty acids have demonstrated a variety of beneficial health effects, such as reducing adiposity and increasing insulin sensitivity in rodents [Storlien *et al*., 1991]. In healthy humans, fish oil has many physiological effects, including a reduction of insulin reaction to oral glucose, without altering the glycaemic response. These fatty acids also decrease sympathetic activation during mental stress and lower the concentration of plasma triglycerides [Delarue *et al*., 2004]. However in patients with type 2 diabetes the involvement of fish oils in their diet remains uncertain, with *n*-3 polyunsaturated fatty acids failing to reverse insulin resistance, but systematically decreasing plasma triglyceride levels [Fickova *et al*., 1998; Durrington *et al*., 2001; Mostad *et al*., 2004]. Nevertheless, in animal models they have been shown to prevent insulin resistance by inducing an alteration in insulin action during a high-fat diet. Indeed, the substitution of *n*-3 LC-PUFA from fish oil for other types of lipids prevents insulin resistance [Oliver, 1997], the mechanisms sustaining such protective effects remain unclear, however, it may be related to the subsequent changes in fatty acid content of the phospholipids found in the membranes of tissues, target by insulin [Petersen & Shulman, 2002]. In muscle, *n*-3 LC-PUFA may improve insulin sensitivity due to an increase in the level of un-saturation of the membrane phospholipids and/or a decrease in muscle content in triglycerides [Kahn & Pedersen, 1993; Zierath *et al.,* 1997]. In adipose tissue, conversely to muscle, the defect in glucose transport induced by a high-fat diet is not affected by *n*-3 LC-PUFA, but may be the result of a reduction in the numbers of insulin receptors and tyrosine kinase activity [Taouis *et al.,* 2002]. In the liver the effect of *n*-3 LC-PUFA may prevent an increase in the activity of the glucose cycle or it may be associated with reduced hepatic fatty acid oxidation, which is known to promote gluconeogenesis [Oakes *et al*., 1997]. Taken together, the results

suggest that *n*-3 LC-PUFA may have a tissue-specific impact in restoring insulin sensitivity.

POLYSATURATED TO SATURATED FATTY ACID RATIO

There is growing evidence that an increase in the level of fat intake in the diet, and more importantly, the relative amounts of saturated and unsaturated fatty acids, plays an important role in the development of insulin resistance [Bray *et al.,* 2002; Harding *et al.,* 2004]. Cross-sectional analysis reported a positive association of saturated fatty acid intake with insulin concentrations, but an inverse association with polyunsaturated fatty acids intake [Ebbesson *et al.*, 2005; Haag & Dippenaar, 2005; Oliver, 1997]. Many studies indicated that one of the most important risk factors for developing type 2 diabetes is a low polyunsaturated to saturated fat ratio (P:S) [Ascherio *et al*., 1999; Harding *et al.,* 2001; Lovejoy, 2002]. For example, in the prospective EPIC-study the energy-adjusted dietary P:S fat ratio was connected with a reduced risk of diabetes, independent of age, sex, family history of diabetes, and other lifestyle factors) [Trichopoulou *et al.,* 2005]. Similar associations were also reported in the United States Nurses' Health Study which showed a significant inverse association between the P:S ratio and the risk of diabetes, with a relative risk of approximately 0.80 for the highest quintile compared with the lowest quintile of dietary P:S ratio [Hu *et al.,* 2001]. In studies where they directly substituted polyunsaturated fat for saturated fat or indirectly substituted monounsaturated fat for saturated fat [Vessby *et al.,* 2001; Summers *et al.,* 2002] they found an improvement in insulin sensitivity following an increase in the P:S ratio. It was clearly confirmed that replacing 5% of energy derived from saturated fatty acids, with energy derived from polyunsaturated fatty acids produced a 43% lower risk of cardiovascular diseases [Hu *et al*., 1997]. Moreover, high levels of P:S ratio was also inversely associated with HbA_{1c} levels [Harding *et al.,* 2001]. Further, long-term (2-7 years) intervention studies relating to ischemic heart disease suggested that increasing the dietary P:S ratio to greater than 1.0 is feasible [Olivier, 1997]. Thus the specific recommendations of these fatty acids should be considered when planning the diabetic diet. Consequently, modifications in the composition of dietary fat may represent a realistic approach for reducing the risk of diabetes in the general population.

N-3 LONG CHAIN POLYUNSATURATED FATTY ACIDS AND CARDIO-VASCULAR RISK IN DIABETIC PATIENTS

The metabolism of *n*-3 fatty acids may explain the cardioprotective effects observed in epidemiological and experimental studies [Delarue *et al.,* 2004; Haag & Dippenaar, 2005; Harding *et. al.,* 2004; Lundgren *et al*., 1989; Panagiotakos *et al.,* 2004; Pérez-Jiménez *et al.,* 2001]. There is evidence that n-3 polyunsaturated fatty acids reduce the level of serum lipids and lipoproteins, impair platelet aggregation, and lower blood pressure. These properties may confer beneficial effects on the risk of type 2 diabetes [Mayer-Davis *et al.,* 1997, Salmerón *et al.,* 2001]. Controlled clinical studies have shown that consumption of n-3 LC-PUFAs has cardioprotective effects in persons with type 2 diabetes, without adverse effects on glucose control and insulin activity. Benefits also include a lower risk of primary cardiac arrest, reduced cardiovascular mortality, particularly sudden cardiac death as well as protective changes of lipid profile [Jarvinen *et al.,* 2006; Pérez-Jiménez *et al.,* 2001; Sanders *et al*., 2006; Simopoulos, 2001]. Studies have suggested that subjects ingesting high *n*-3 fatty acids produced a reduction in the level of serum triglyceride and increased high-density lipoprotein, a lipoprotein which is positively associated with cardiovascular disease [Delarue *et al.,* 2004; Harding *et al.,* 2004; Panagiotakos *et al*., 2004; Sanders *et al*., 2006]. More over *n*-3 fatty acids decreased the risk of atherosclerosis and the consequences of this disease by improving endothelial function, reducing platelet aggregability and lowering blood pressure [Haag & Dippenaar, 2005; Pérez-Jiménez *et al.,* 2001]. These favorable effects outweigh the modest increase in low-density lipoprotein levels that may result from increased *n*-3 LC-PUFA intake [Nettleton & Katz, 2005].

MOLECULAR EVIDENCE

The evidence of polyunsaturated acids' beneficial effects are described, not only in epidemiological studies but also many molecular studies have shown their advantageous influence on cellular membranes, as membrane lipid structure are regulated by the composition of fatty acids derived from the diet [Summers *et al.,* 2002]. The protective effect of unsaturated fatty acid was established a long time ago by using the hyperinsulinaemic, euglycaemic clamp technique, (HECT) for measuring insulin sensitivity. The diet high in *n*-3, with a low *n*-6/*n*-3 ratio, maintained insulin action at normal levels [Boden, 2003; Bray *et al*., 2002; Delarue *et al.,* 2004; Fickova *et al.,* 1998; Jucker *et al*., 1999]. Thus, the lipid profile of membranes is sensitive to dietary derived *n*-3 and *n*-6 polyunsaturated fatty acids, and prefers to incorporate more *n*-3's than *n*-6's. Therefore improvements in insulin action is as a result of increasing the content of polyunsaturated fatty acids, particularly those containing 20–22 carbons, and especially if these belonging to the *n*-3 fatty acid family [Feskens & van Dam, 1999; Hulbert *et al*., 2005; Simopoulos, 2001].

The *n*-3 long chain polyunsaturated fatty acids (*n*-3 LC-PUFA) also prevent the depletion of the glucose transporter protein isoform 4 (GLUT-4), in muscle and adipose tissue [Long & Pekala, 1996; Zierath *et al.,* 1997]. This effect is mainly due to EPA which can be metabolized to anti-inflammatory prostaglandins, from the 3-series. Another fatty acid from the same series, DHA, cannot be converted to a prostaglandin; however it can undergo the retro-conversion to EPA, and thence formation of a 3-series prostaglandin [Gibney *et al*., 2005]. Theses eicosanoids seem to play a very important role in regulation of the GLUT-isoform 4, by effecting the trafficking of insulin and thus insulin-stimulated glucose transport [Abel, 2004]. Physiologically, insulin rapidly stimulates glucose transport, primarily by inducing the translocation of vesicles containing GLUT-4 from intracellular pools to the plasma membrane [Parillo *et al*., 1992; Zierath *et al*., 1997]. As a result of this action insulin-stimulated glucose uptake (ISGU) is achieved [Wilkes *et al.,* 1998]. In isolated

adipocytes, *n*-3 LC-PUFA modulate ISGU by increasing its activity [Parillo *et al*., 1992]. Conversely, a high fat diet with 30% of saturated fatty acids causes defects in the GLUT-4 trafficking process in rodent models [Kahn & Pedersen, 1993]. Some authors suggest that probably the defective GLUT-4 transport alters insulin signaling, but not its synthesis [Pryor *et al.,* 2000]. However another study revealed the protective effect of *n*-3 polyunsaturated fatty acids in preventing insulin resistance during ingestion of a high fat diet, even when the depletion of the glucose transporter protein GLUT-4 in muscle was observed. The *n*-3 LC-PUFA also decreases muscle intra-myofibrillar triglyceride levels and liver steatosis, with this effect resulting from a decreased expression of lipogenesis enzymes and delta 9-desaturase [Delarue *et al.,* 2004].

FUTURE AIM: PPAR

Many studies of the last decade have revealed that the key regulators in the development of insulin resistance are the peroxisome proliferator-activated receptor-gamma transcription factors (PPAR gamma) [Chambrier *et al*., 2002; Ide *et al.,* 2004; Kliewer *et al.,* 1997; Price *et al*., 2000]. These factors are from the nuclear receptor superfamily, the PPARs heterodimerize with the 9-*cis*-retinoic acid receptor. They bind to specific response elements in the promoter regions of target genes to change their transcription rate; they also take part in the regulation of adipocyte differentiation and adipose tissue lipid metabolism [Kliewer *et al*., 1997]. PPAR gamma transcription factors act as nutrient sensors [ADA, 2004] and are expressed at their highest concentrations in adipose tissue and at their lower concentrations in liver and muscle [Tontonoz *et al*., 1994]. Mutation-related impairment of these factors can result in insulin resistance and type 2 diabetes. Many studies suggest that the composition of dietary lipids may affect PPAR gamma gene expression. Usually they support the concept that polyunsaturated fatty acids can act as ligands of PPAR gamma or modulate their expression, thus increasing transcription and synthesis of GLUT-4 and improving insulin sensitivity [Chambrier *et al*., 2002; Ide *et al.,* 2004; Kliewer *et al.*, 1997]. Chambrier *et al.* [2002] demonstrated that EPA significantly increases mRNA levels of type-1 PPAR gamma, in isolated human adipocytes and this effect was dependent on its concentration. In addition, a strong positive correlation was found between plasma EPA concentrations and PPAR gamma mRNA levels in adipose tissue of obese subjects.

Dietary fat may also affect PPAR alpha gene expression [Kliewer *et al*., 1997; Price *et al*., 2000]. PPAR-alpha are nutrient sensors which play an important role in insulin resistance. The stimulation of PPAR-alpha inhibits lipid accumulation and improves insulin signaling [Ye *et al*., 2001]. Sethi and colleagues [2002] demonstrated that oxidized, but not native un-oxidized EPA can potently activate PPAR-alpha. In rodent models *in vivo*, oxidized EPA markedly reduced leukocyte rolling and adhesion to ventricular endothelium *via* a PPAR-alpha-dependent mechanism. Many studies suggested that the beneficial effects of *n*-3 polyunsaturated fatty acids may be also explained by a PPAR-alpha-mediated anti-inflammatory effect of oxidized EPA [Kliewer *et al.,* 1997; Ye *et al*., 2001].

CENTRAL MODULATION

The description of the *n*-3 fatty acid would not be complete without mention of their role in central nervous system in the diabetic state. The intake of nutritional components is regulated by nerve centers located in the ventromedial (feeding) and dorsolateral (satiety) centre in hypothalamic areas. These centers are also influenced by dietary fatty acid profile. It was demonstrated that intake of saturated fats by mice increased neuronal activity in their feeding centre, whereas *n*-3 LC-PUFA feeding increased satiety centre activity [Wang *et al.,* 1999]. The anti-adiposity role of *n*-3 LC-PUFAs is explained by the action of leptin – one of the adipocyokines secreted from adipocytes. Leptin acts on the arcuate nucleus to block secretion of the obesogenic neuropeptide Y, thus increasing satiety. Increasing the level of *n*-3 LC-PUFA in the diet can lead to increased plasma leptin levels when compared with a diet rich in saturated fats. The evidence supporting the anti-adiposity role of *n*-3 LC-PUFAs should be a factor that is considered when planning diets, of usually overfeed patients with type 2 diabetes [Kratz *et al.,* 2002].

Preliminary evidence suggests increased consumption of *n*-3 LC-PUFAs together with a reduced intake of saturated fat may reduce the risk of developing type 2 diabetes from impaired glucose tolerance in overweight subjects [WHO, 2003b]. Expected health benefits and public health implications of consuming 1 to 2 g/day *n*-3 LC-PUFA, as part of lifestyle modification in insulin resistance and type 2 diabetes, are currently viewed as nutritional recommendations [Nettleton & Katz, 2005; Simopoulos, 2001].

CONCLUSION

Increased consumption of more energy-dense, nutrient-poor foods with high levels of animal fats, combined with reduced physical activity, have led to increase numbers of obese people and its consequence of type 2 diabetes [ADA, 2004; Colditz *et al.,* 1995; Kemper *et al*., 2004; Wild *et al.,* 2004]. Proper diet, as well as physical activity is also the mainstay of non-pharmacological diabetes treatment recommended by The World Health Organization [Kemper *et al.*, 2004, WHO, 2003b]. Such diets should be rich in breakfast cereals, fish, fruit, spreadable fats rich in polyunsaturated fatty acids, nuts, and vegetables, and low in alcoholic beverages, eggs, milk, processed meat, and sugars [Bray *et al.,* 2002; de Lorgeril *et al.,* 1999; Feskens *et al.,* 1995; Panagiotakos *et al*., 2004; Skrha *et al.,* 2005]. The increased amount of *n*-3 polyunsaturated fatty acids in daily food rations seem to have beneficial affects on insulin sensitivity and can lead to a reduced risk of diabetes [Ebebesson *et al*., 2005; Lovejoy, 2002; McGarry, 2002; Nettleton & Katz, 2005]. However the American Heart Association does not distinguish between *n*-6 and *n*-3 fatty acids, proposing a prudent low-fat diet [ADA, 2004]. Unfortunately the Western diet is deplete in *n*-3 fatty acids, while the widespread use of inexpensive vegetable oils, rich in *n*-6 PUFAs, have resulted in very unfavorable ratios of *n*-6/*n*-3 of 20:1 and higher [Nettleton & Katz, 2005]. Contemporary societies should come back to the modified Crete diet, which clearly reduces the risk for coronary heart disease and

cancer and contains more polyunsaturated fatty acids with a much improved *n*-6/*n*-3 ratio [Panagiotakos *et al.,* 2004; Pérez-Jiménez *et al.,* 2001; Simopoulos, 2001].

Thus, we need a greater understanding of the role played by dietary fat and plasma fatty acids in the pathogenesis of insulin resistance so that we can better prevent and improve future treatment. However today we can conclude that effective treatment for individuals and groups at risk of developing diabetes mellitus is based on proper diet, weight loss and management of co-morbidities. The *n*-3 family of polyunsaturated fatty acids can support the difficult treatment of subjects with type 2 diabetes and one important conclusion from this review is that both total fat and individual fatty acids have to be considered when reaching conclusions about dietary fat and diabetes mellitus.

ACKNOWLEDGEMENT

This paper has been written during the Scholarship found by Ernst Schering Foundation at the Department of Medicine, Nutrition and Metabolism Group, The Queen's University of Belfast.

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Received July 2009. Revision received and accepted February 2010.