LL 1

Diabetes and Internet

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Many controlled clinical trials have shown that maintaining the appropriate HbA1c level reduced the risk of diabetic chronic complications in people with type 1 and type 2 diabetes mellitus. However, data from the "National Health and Nutrition Examination Surveys" showed that the glycemic control did not change at all until recently in real practice. These data suggest new approaches are urgently needed to achieve and maintain the target to treat to reduce the serious chronic diabetic complications. For achievement of ideal glycemic control in diabetic patients, intimate doctor-patient relationship and individualized care and education is essential. And this very close communications between health care providers and the patients with diabetes should be lifelong and consistent. However it is almost impossible in the current "face-to-face" treated medical system.

The internet is a worldwide communication system that allows a person to contact with others anywhere at anytime. So, whenever diabetic patients want to contact with their providers they can get information using internet. Korea is one of the most developed countries in the fields of internet-network. Nearly all the families have their own computers and can access the internet via modem or high speed network system. So, we designed the web-based diabetic patients' management system so call "Internet Based glucose monitoring system" (IBGMS) instead of standard face-to-face doctor-patients interview in the hospital.

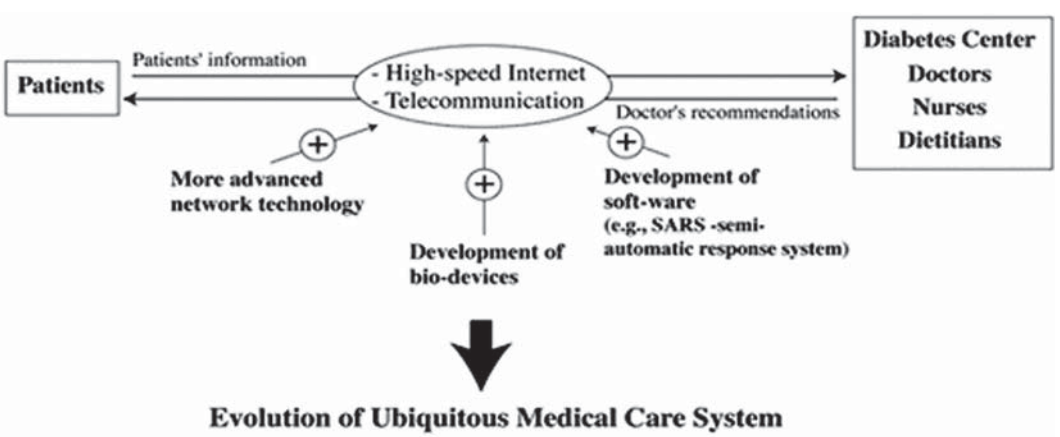

Fig. 1 The scheme of IBGMS

1. Establishment of IBGMS

The scheme of IBGMS is illustrated in Fig 1. Patients logged on the website (www.biodang.com) from their homes or offices at a time they found convenient and uploaded their glucose levels (SMBG results) on a blood glucose board of the on-line chart (IBGMS chart in the website www.biodang.com) and their additional information such as current drug information (the type and dosage of oral hypoglycemic medications or insulin), lifestyle modifications, hypoglycemic events, and questions. In addition, patients recorded in the memo box any changes in their blood pressure or weight, and any questions or detailed information that the patient wished to discuss, such as changes in diet, exercise, hypoglycemic events, and other factors that might influence the blood glucose level. The staff participating in the Internet-based system included three endocrinologists (a professor and two clinical instructors), a nurse, and a dietician. The two clinical instructors

logged onto the system daily and sent appropriate recommendations (based on the patients' uploaded blood glucose data) to each patient in the intervention group every 2 weeks. The recommendations were made according to the Staged Diabetes Management Guidelines in Korea. The instructors also replied on-line immediately to any submitted questions about medication or hypoglycemic episodes. We did not adopt any other automated algorithms during the study. If there was any need to change the patient's medications or dosage, the clinical instructors referred the case to the professor. Any additional specific problems about self-management or life-style changes were referred to the nurse or dietician. In the off-line system, patients visited the outpatient clinic every 3 months where they had a face-to-face interview with their physician and provided a blood sample for follow-up laboratory testing. This system formed an electronically organized, Internet-based clinical circuit for diabetes management.

2. Patient's enrollment and education for applying the IBGMS in clinical practice

Patients who were diagnosed as diabetes mellitus for at least 1 year were recruited from the home page of Kangnam St. Mary's Hospital on the web from July to September, 2000. We recruited all participants who had internet access in their homes for web-based diabetes management system. Ethics committee approval was obtained from our institution and review board of Korea institution for social and health affair.

At the first visit to Kangnam St. Marys Hospital in Seoul, following information was recorded for each participant; age, height, weight, past medical history, family history and social history like smoking and alcoholic drinking. Laboratory tests for fasting blood glucose, lipid profiles, glycated hemoglobin (HbA1c) and other tests for renal and liver function was done after overnight fast. Total fat and muscle amount of participants was also analyzed. All participants interviewed with nurses for detailed information including duration of diabetes, current medication and dosage. Then, they received education for access and use of specialized web-based diabetic patients management system. During study period, all participants could contact with their health providers though specialized electronic chart on the web. And they received recommendation about diabetes management such as dosage adjustment of medication, correction of life styles including diet and exercise and general information about diabetes. After 3 months, all participants revisited to the hospital for examination to compare with previous data before start of the study and received survey of satisfaction with web-based diabetes management system. A total of 185 diabetic patients (male; 132, female; 53) were participated and the mean age of participants was 42.4 years old (4-79 years old). Mean duration of diabetes in our participants was 5.0?5.9 years (0-30 years). Although almost half of participants lived in Seoul where our hospital is located, many diabetic patients who lived other region engaged in our study.

3. Patient's compliance, satisfaction and the effects of IBGMS on glycemic control

Changes of biochemical variables before and after the study period in study subjects were monitored. The mean HbA1c was improved from 7.5±1.5% to 7.0±1.1% after using the management program (p=0.003). Especillaly, in the patients with the HbA1c of 7% or higher at baseline, mean HbA1c were much improved from 8.4±1.2% to 7.5±1.0% after the study (p=0.010). The mean serum triglyceride and HDL-cholesterol levels after using the program was also decreased significantly compared with levels at baseline. Overall compliance in participants in our study was 72% three months later. Patients of good compliance were older age and had more duration of diabetes compared with that of poor compliance. We also surveyed satisfaction about program in our study subjects. Most participants were satisfied with this web-based diabetic patient's management program.

4. Randomized controlled trial for short-term effects of IBGMS

We conducted a randomized clinical trial involving 110 patients who visited to outpatients clinic at the Kangnam St. Mary's Hospital for 3 months. The study subjects were treated with IBGMS for 12 weeks and the control group received the usual outpatient management over the same period. HbA1c and other laboratory tests were performed at baseline and at the study close. At baseline no significant differences were found between the two groups with respect to age, sex, diabetes duration, BMI, blood pressure, HbA1c and other laboratory data. In the follow up test, the study group showed a significant reduction in HbA1c by 7.1% (0.54% absolute, P=0.001), while the control group showed a greater HbA1c increase (P=0.054). Moreover,

there was a remarkable reduction of HbA1c by 11.1% (0.92% absolute, P <0.001) in the patients with HbA1c ? 7.0% in the study group and those with HbA1c <7.0% maintained a good level of HbA1c of 6.32% at the study close. This new IBGMS resulted in a significant reduction of HbA1c during the study period. We propose that this IBDMS be used as a new method of diabetes control.

5. Randomized controlled trial for long-term effects of IBGMS

We also conducted a prospective randomized clinical trial involving 80 diabetic patients at the outpatient clinic. The intervention group treated using an internet-based glucose monitoring system for 30 months, while the control group received conventional outpatient management. Mean HbA1c and stability of glycemic control in intervention group for study period were significantly lower than those of the control group. The internet-based glucose monitoring system appears to be effective tools for achieving the tight blood glucose control and stabilized glycemic fluctuation over 30 months.

Conclusion and future directions

IBGMS could improve the glycemic control and additionally reduced the medical cost. However, the open loop from the patients to the doctor in our system induced the heavy burden of the cost, recently, we have been developing the new staged management system comprised by the software to analyze and report the patient's SMBG data bidirectional manner which we named SARS (semi-automatic response system) and primary screening step by diabetes specific nurse. IBGMS combined with SARS could be implemented in real clinical practice with very high cost-effectiveness.

In conclusion, we confirmed the long-term effectiveness of the IBGMS and furthermore developed second generation of IBGMS guided the patients at any time and any where by a newly developed mobile device. We expect that the second generation of IBGMS will be adopted by more diabetes centers throughout the world and ultimately will contribute to reducing complications and improving quality of life in patients with diabetes.

Full text. e-Journal: *http://www.medassocthai.org/journal*

LL 2

Diabetes Dyslipidemia 2005

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Patients with type 2 diabetes have a risk of dying from cardiovascular disease that is 2-4 times greater than those without diabetes. In part, this relates to the presence of a dyslipidaemia characterized by an elevated concentration of plasma triglyceride and a reduced concentration of high density lipoprotein (HDL) cholesterol. The concentration of low density lipoprotein (LDL) cholesterol in diabetic patients is no different from that in the non-diabetic population, although the LDL fraction in diabetics is characterized by an increased proportion of small, dense particles. The HDL particles in diabetic patients tend also to be smaller and denser than normal. The concentration of apoB is increased and that of apoA-I is reduced in diabetic as compared with non-diabetic subjects. Each of these components of diabetic dyslipidaemia has the capacity to increase the risk of developing cardiovascular disease.

The hypertiglyceridemia in diabetic patients is often associated with an increased concentration of remnant particles that are known to be atherogenic. Small, dense LDL particles have an increased susceptibility to oxidation and are thus more atherogenic than larger and less dense LDL particles. And the increase in concentration of apoB indicates an increase in the number of potentially atherogenic apoB-containing lipoproteins circulating in plasma. These abnormalities, combined with a reduction in the concentration of protective HDL particles, greatly increase cardiovascular risk.

Potential agents for treating diabetic dyslipidaemia include statins, fibrates and nicotinic acid. Statins reduce the concentration of apoB-containing particles and, to a lesser degree, also plasma triglyceride; they also have a moderate ability to raise HDL cholesterol. Fibrates reduce plasma triglyceride, increase HDL cholesterol and increase LDL particle size. Nicotinic acid reduces plasma triglyceride and raises HDL cholesterol, although it has the potential to increase insulin resistance in diabetic subjects. Improved glycaemic control is also important and may contribute both to a reduction in plasma triglyceride and an increase in HDL cholesterol.

There is now strong evidence from large-scale, hard end-point trials that both statins and fibrates reduce cardiovascular events in patients with diabetes.

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LL 3

Advances in the Treatment of Diabetic Foot Ulcers

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The foundation of appropriate and successful care of the diabetic foot has always been based on reduction of repetitive trauma through off-loading the neuropathic foot. However, even with adequate off-loading, a significant number of ulcers fail to respond to care or do so at a relatively slow rate, resulting in continued tissue breakdown, infection, amputation and increased associated morbidity and mortality. Advances in the treatment of wounds, particularly diabetic foot ulcers, has resulted in newer treatment modalities which may assist in expediting wound closure, thereby reducing serious complications associated with the diabetic foot.

Interestingly, despite the rapid rise of diabetes, approaching epidemic proportions worldwide, little to no attention is given to the diabetic foot at national and internation diabetes conferences. Yet of the greater than 50% of amputations in the United States performed on diabetics, greater than 70% of these amputations are the result of a diabetic foot ulcer. As the point prevalence of diabetes increases around the globe, one will evidence a parallel increase in diabetic foot ulcers and amputations of the diabetic lower extremity.

The goal of this presentation is to present the respected audience with an overview of the scope of diabetic foot ulcers, the difficulties confronted in administering care, and alternative treatments that may assist in providing more advanced, appropriate and successful approaches to treatment. It is my hope that this presentation will stimulate the clinicians treating these problematic wounds, to further explore the advances in the treatment of diabetic foot ulcers that are now available.

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LL 4

Global Impact of Diabetes

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In 2003, the IDF Atlas estimated that 194 million people or 5.1 % of the world's adult population suffered from diabetes (90-95% having type 2 diabetes). The projections are that by 2025 this number will rise to 334 million people or 6.3% of the global adult population. In some countries the prevalence of diabetes is significantly greater (eg Nauru 30%, United Arab Emirates 20.1%, Bahrain 14.9%).

In contrast, there are approximately 430,000 children <15 years of age with type 1 diabetes globally, with 65,000 new cases diagnosed each year. Despite these lower numbers, the direct costs of type 1 diabetes are also very considerable because the high likelihood of complications occurring in adulthood due to the long duration of their diabetes.

In 2004 the WHO announced that diabetes had overtaken HIV/AIDS as the largest single killer (3.2 million versus 3 million per year) and for the first time a non-communicable disease has overtaken an infectious disease as the single most important cause of global mortality.

Childhood and adolescent type 2 diabetes is occurring more frequently, especially in high risk populations (eg Arizona Pima Indians, Australian Torres Strait Islanders). In the USA and Australia, clinic data suggests that type 2 diabetes is now responsible for up to 20-40% of new diagnoses in adolescence. Approximately 30% are insulin requiring and the health care utilisation costs (clinic visits) are just as high as for type 1 diabetes. Data from 13 countries in the Western Pacific Region have shown that insulin-requiring type 2 diabetes in adolescence is just as difficult to treat as type 1 diabetes with similar mean HbA1c levels being attained.

The costs of diabetes are increasing at such a rate that they threaten to overwhelm health care budgets. Most developed countries spend 8-12% of their health care budgets on direct health care costs of diabetes. The IDF estimates that the annual direct healthcare costs of diabetes worldwide, for people in the 20-79 age bracket, is at least 153 billion international dollars, and may be as much as 286 billion, or even more. The indirect costs of diabetes (loss of productivity) vary greatly and in developing countries may be 2-5 fold greater than direct costs. No-one can quantify the intangible (suffering) costs of diabetes, but with a million amputations occurring because of diabetes annually, with diabetes being a leading cause of end-stage renal failure and with 5% of the world's blindness attributed to diabetic retinopathy, the humanitarian costs are indeed high.

The projected annual increase of 6 million in the global prevalence of diabetes has major health work force implications, especially for developing countries where there is already an acute shortage of doctors. With increases in the prevalence of diabetes in the order of 100% over the next 20 years, traditional health delivery models of doctors providing most aspects of diabetes care become increasingly unsustainable. In many developing countries, there is a shortage of diabetes educators and currently up to 70% of diabetes education is being delivered by doctors. New models of health care delivery are needed with increasing reliance on allied health workers (nurses and other non-medical health care professionals). Diabetes educators (predominantly, but not exclusively, nurse educators) will need to be trained to deliver much of the education and non-acute medical care currently provided by doctors.

Non-communicable diseases are generally chronic diseases with intermittent acute illness phases. Most health care systems are focused on treating the acute illness phase with little emphasis on prevention of the disease in the first place and little emphasis on preventing or retarding the progression of complications of the disease. For diabetes this paradigm of health care delivery with its emphasis on acute illness will result in health care budgets being overwhelmed.

Health care systems urgently need to develop models of chronic care delivery aimed at prevention of diabetes complications and to focus on population approaches to the prevention of diabetes itself.

Wild S, Roglic G, Green A, Sicree R, King H, Global Prevalence of Diabetes, Diabetes Care *27:1047-1053.*

Diabetes Atlas second edition, International Diabetes Federation, 2003

Full text. e-Journal: *http://www.medassocthai.org/journal*

LL 5

Metabolic Syndrome and Adipocyte-Derived Factors

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The metabolic syndrome clusters elevated blood pressure, dyslipidemia, and insulin resistance in each individual, and is a common cause of cardiovascular diseases also in Eastern Asians. In 2005, IDF designated the metabolic syndrome as central (visceral) obesity represented by an increase of waist circumference plus 2 or more co-morbidities. Visceral fat locates upstream of liver and has high lipogenic and lipolytic activities. Free fatty acids and glycerol derived from visceral fat go into the liver via portal vein, and are used for VLDL synthesis and gluconeogenesis, respectively.

To elucidate the molecular links between visceral fat and the metabolic syndrome, we performed systemic analysis of the expressed genes in human adipose tissue, and found adipose tissue, especially visceral fat tissue, expressed a variety of the genes for bioactive secretory proteins including growth factors, cytokines and complement factors in the immune system. We conceptualized these adipose-derived factors as 'adipocytokines'. Adipose tissue produces proinflammatory cytokines such as IL6 and TNFalpha, and prothrombotic factors such as PAI-1. Through this search, we discovered a novel adipose-specific protein named 'adiponectin'. Adiponectin is circulating in plasma but its level is decreased in visceral fat accumulation. Both experimental and clinical researches suggested that adiponectin protects against atherosclerosis, and might play an important role in the metabolic syndrome. I will present current advances of adiponectin and visceral obesity researches in our laboratory, and also talk on our current finding of the glycerol channel molecule in adipose tissue.

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LL 6

Standardisation of HbA_{1c}: What can We Expect?

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HbA_{1c} is the gold standard for assessment of glycaemic control in patients with diabetes. Following the Direct Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) HbA_{1c} can be used to predict the risk of development of complications in people with type 1 and type 2 diabetes. Today, HbA_{1c} is used for treatment goals and as a target for therapeutic intervention. Hence, harmonisation of HbA_{1c} results has become necessary. National HbA_{1c} standardisation programmes in USA [National Glycohaemoglobin Standardisation Programme (NGSP)], Japan [Japanese Diabetes Society (JDS) in collaboration with the Japanese Society of Clinical Chemistry (JSCC)] and Sweden in the mid to late 1990s improved the quality of HbA_{1c} assays in clinical use. The methods used in these standardisation programmes are not primary reference methods but are direct comparison methods (DCMs) and are not truly specific for HbA_{1c}. In 1994 the International Federation of Clinical Chemistry (IFCC) established a working group on standardisation of HbA_{1c}. This working group has developed a global HbA_{1c} reference system, prepared pure HbA_0 and HbA_{1c} as the primary reference material, developed a reference method, installed a network of reference laboratories, and prepared secondary reference material. HbA_{1c} has been defined as ,-N-valine glycated haemoglobin (,-N-(1-deoxy)-fructosyl-haemoglobin). The reference method is based on two-dimensional peptide mapping after proteolytic cleavage with endoprotease Glu-C, then separation of the resulting glycated and non-glycated N-terminal hexapeptides by reversed-phase HPLC followed by quantification by mass spectrometry or by capillary electrophoresis. Considering the lack of specificity of the DCMs used in the standardisation programmes in USA, Japan and Sweden, it is not surprising that the HbA_{1c} results generated by these DCMs are significantly higher than the results produced by the IFCC reference method. Correlations between the IFCC reference method and the DCMs have yielded the following master equations: NGSP-HbA_{1c} = 0.915(IFCC-HbA_{1c}) + 2.15% (r^2 = 0.998); JDS/JSCC-HbA_{1c} = 0.927(IFCC-HbA_{1c}) + 1.73% (r^2 = 0.997); Swedish-HbA_{1c} = 0.989(IFCC-HbA_{1c}) + 0.88% (r^2 = 0.996). There are several reasons why the IFCC reference method should be used by both manufacturers and DCM schemes. The In-Vitro Diagnostic (IVD) Directive concerning medical devices in Europe states that diagnostic manufacturers must guarantee the traceability of their routine measurements to reference methods and materials of higher metrological order. This implies that manufacturers must calibrate using IFCC methodology, being the reference method of higher metrological order. A second reason for change is to improve globally the quality of HbA_{1c} assays. A third reason for changing to the IFCC-HbA_{1c} reference system is the opportunity to introduce a unique reporting system for HbA_{1c} globally. An option would be to use the IFCC reference system and convert the IFCC values to the well understood DCCT-aligned values. A second possibility is to report the lower IFCC-HbA_{1c} values, in general being about 2% lower than the DCCT values with a reference range of 3-4%. Introduction of the lower IFCC-HbA_{1c} values may lead to misinterpretation of the degree of glycaemic control. With regards to a new reporting system two possibilities have been discussed: reporting HbA_{1c} as mean blood glucose (MBG) or reporting in SI units, e.g. mmol HbA_{1c} per mol HbA. A number of correlation studies have shown that MBG can be correlated to HbA_{1c} but there is a large dispersion of the results around the regression line. Hence, a large uncertainty is introduced, thus defeating the purpose of introducing the new precise IFCC standardisation process. Reporting HbA_{1c} in mmol HbA_{1c} per mol HbA introduces a totally new reference interval (reference range 30 – 40). No confusion will exist between the current DCM and the new IFCC results. A meeting was held in London on 20 January 2004 amongst the IDF, EASD and ADA with the Chairman of the IFCC HbA_{1c} working group and a representative of NGSP. This International Diabetes Workgroup agreed that the IFCC Reference Method should become the global reference standard and that all manufacturers should now calibrate to the new method. The name change of the assay to reflect MBG was accepted. The relationship between HbA_{1c} and MBG established from the DCCT is MBG mmol/L = 1.84 x IFCC-HbA_{1c}. With the IFCC-

HbA_{1c} standardistion the analytical performance of routine HbA_{1c} assays will be improved. The analytical goal is a within and between run CV of 2%, leading to an HbA_{1c} difference between results of 0.5% to be considered a significant change. If this can be achieved, it may be possible to incorporate HbA_{1c} into the diagnostic strategies for diabetes mellitus.

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LL 7

Impact of Intracellular Stress On Diabetes and Its Complications

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Intracellular stresses, such as oxidative stress and endoplasmic reticulum (ER) stress, are know to involve in the development and progression of various diseases including atherosclerosis, neurodegenerative disorders and diabetes. In this lecture, our recent studies about the impacts of ER stress and reactive oxygen species derived from mitochondria (mtROS) on diabetes and its complications will be presented. The ER serves important functions, including post-translational modification, folding, and assembly of secretory proteins, and its function is essential to cell survival. Various conditions that interfere with ER function are called ER stress. We have found that NO-induced apoptosis in beta -cells is mediated by ER-stress pathway. NO causes ER stress and leads to apoptosis through induction of ER stress-associated apoptosis factor CHOP. The Akita mouse with a missense mutation (Cys96Tyr) in the insulin 2 gene develops diabetes with a reduced beta -cell mass. This mutation disrupts a disulfide bond of insulin and may induce ER stress. Overexpression of the mutant insulin in mouse MIN6 beta -cells induced CHOP expression and led to apoptosis. Targeted disruption of the CHOP gene protected islet cells from apoptosis and delayed the onset of diabetes in the heterozygous Akita mice. In addition, db/db mice displayed an increase of CHOP and other ER stress related genes suggesting the involvement of ER stress in the progression of diabetes in the mice. These results imply the importance of ER stress pathway in beta-cell function both in type 1 and type 2 diabetes. The mtROS is reported to play primary role in the development of diabetic complications. In MIN6 cells, hyperglycemia increased mtROS production, and the treatment of the beta-cells with H_2O_2, a chemical substitute for ROS, suppressed the first phase of glucose induced insulin secretion. This was partly explained by the suppression of GAPDH activity through ROS. On the other hand, in human hepatoma Huh7 cells, mtROS decreased the tyrosine phosphorylation of IRS-1, an important mediator of insulin signal, via the activation of ASK-1 – JNK pathway. Therefore, mtROS was suggested to prevent insulin secretion and action, which may explain glucotoxicity observed in diabetes. To further study the role of mtROS in diabetic complications, we created a transgenic (eMnSOD-Tg) mouse that overexpresses MnSOD in endothelial cells, and examined the impact of mtROS on diabetic retinopathy. Increased expression of VEGF and fibronectin mRNAs in retinas observed in streptozotocin (STZ)-induced diabetic WT mice was completely prevented in retinas of STZ-induced diabetic eMnSOD-Tg mice. In the relative hypoxia-induced in vivo *retinopathy model, retinal flat-mount pictures showed typical central avascular areas in WT mice. However, in eMnSOD-Tg mice, avascular areas were significantly reduced. In addition, microaneurysm formation observed in WT mice was reduced by 70% in eMnSOD-Tg mice. Therefore, normalizing hyperglycemia-induced mtROS could prevent diabetic retinopathy* in vivo*. Our results indicate that intracellular stress is a novel target for prevention and treatment of diabetes and its complications.*

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LL 8

Insulin Pump Therapy: Pesent and Future Perspective

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Insulin pump therapy (usually meaning continuous subcutaneous insulin infusion, CSII) achieves strict glycaemic control in selected type 1 diabetic subjects by administering short-acting (monomeric) insulin at variable infusion rates from a portable pump. Its routine use is increasing throughout the world (now about 20% of type 1 patients in the USA), though many countries have had low uptake to date.

The best evidence-based indication for CSII is frequent, unpredictable hypoglycemia, in spite of best attempts with multiple daily insulin injections (MDI), and this is now incorporated into several national guidelines.

Meta-analysis shows that in general type 1 diabetic patients, the difference in HbA1c on CSII vs. MDI is relatively small (~0.5%) but in hypoglycaemia-prone diabetic subjects, the fall in HbA1c is greater than expected (~1.5%), with the largest reduction in those with the worst control on MDI. Within-day and between-day blood glucose variability is also significantly reduced on switching from MDI to CSII. The effectiveness of pump therapy in hypoglycaemia-prone subjects might be due to the difficulty of improving control with MDI in such difficult patients, who resist measures that might precipitate further hypoglycemia. In our hands, MDI based on glargine was not more effective than isophane-based MDI and significantly worse than CSII.

In addition to a reduction in hypoglycaemia and improved perception of quality of life, the clinical impact of pump therapy includes a major reduction in the risk of developing microvascular disease. We estimate that about 5% of type 1 diabetic patients have severe hypoglycaemia and 15% a highly elevated HbA1c (>9.5%) on MDI. Taking into account that some patients are unsuitable for pump therapy, the target percentage might therefore be about 15-20% of type 1 diabetic subjects. So far there is little evidence that CSII is more effective than MDI in type 2 diabetes, but this group needs further study.

We expect increasing use of 'smart pumps' in the next few years which can, for example, calculate the bolus dose based on food intake and blood glucose level. Continuous in vivo glucose sensing is now established in clinical practice, at least in the short term, and attempts are being made to couple glucose sensors to insulin pumps so that in the future a closed-loop system can be used in clinical practice.

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