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Genetic Testing of Newborns for Type 1 Diabetes Susceptibility – The MIDIA Study

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1. Introduction

Type 1 Diabetes (T1D) is one of the most common chronic diseases with childhood onset, and the disease has increased two to threefold over the past half century by yet unknown means. Recently it was showed that if the present trend continues, the prevalence of cases younger than 5 years of age will rise by 70% within year 2020 (Patterson et al., 2009).

1.1 Background and status of knowledge

Type 1 Diabetes (T1D) is a T-cell mediated autoimmune disease that develops in genetically susceptible individuals whose immune system destroys the majority of insulin-secreting β-cells in pancreatic islets (Eizirik et al., 2009). The incidence of T1D has increased more than two- to threefold over the past half century, the most striking example being Finland where it has risen from 12 to 63/100,000 (Knip & Siljander, 2008; Patterson et al., 2009). This increase in incidence has not been paralleled by an increase in the frequency of major risk genes, including HLA class II, insulin, PTPN22, CTLA-4 and IL2RA (Barrett et al., 2009). Indeed, the prevalence of the classical HLA class II genes, which account for approximately 40% of genetic risk, appears to be decreasing (Gillespie et al., 2004; Fourlanos et al., 2008). There are now more than 40 risk loci associated with T1D with the majority of non-HLA genes displaying odds ratio <1.2. (Barrett et al., 2009). Moreover, most individuals who possess T1D risk genes do not develop the disease. Importantly, the concordance rate among monozygotic twins ranges from as low as 25 to 65% (Redendo et al., 1999, 2008; Hyttinen et al., 2003) and is approximately 6% in siblings. A common explanation has been that changes in environment must contribute to the increase in the disease. In particular, environmental exposures to dietary antigens and microbes have been implicated (Knip et al., 2005; Lefebvre et al., 2006). However, no single pathogenic environmental agent has been identified that explain all cases. In all likelihood, T1D develops by various combinations of pathways in response to commonly encountered environmental exposures.

1.2 Nutritional related factors and type 1 diabetes risk

The Norwegian Institute of Public Health is currently running two large prospective cohort studies; "Environmental Triggers of Type 1 Diabetes" (MIDIA) (www.fhi.no/midia) and "The Norwegian Mother and Child Cohort Study" (MoBa) (www.fhi.no/morogbarn). In MIDIA we will be able to study the impact of the dietary intake in children as well as

mothers during the breast-feeding period and in MoBa we will be able to study the dietary intake of the mother during pregnancy for development of T1D in the child. These two studies will be linked to allow several approaches to be tested in the role of early diet and development of T1D. In the MIDIA study newborns have been identified by testing for the high-risk genotype (DRB1*03-DQA1*05-DQB1*02/ DRB1*04:01-DQA1*03-DQB1*03:02) in the HLA-system (Cinek et al., 2000). The MIDIA study is unique compared to the few other ongoing worldwide cohorts because of pregnancy data from the Norwegian Mother and Child Cohort Study (MoBa). Information from questionnaires, public records as well as blood samples from mothers (twice during pregnancy) and children (cord blood) have been collected from 107,000 pregnancies (Magnus et al., 2006; Rønningen et al., 2006). 50% of the children participating in MIDIA have a mother who also participates in MoBa, and consent has been given for linking information from the two studies and using biological specimens (Stene et al., 2007).

1.2.1 Foetal exposure and early life exposure to nutritional factors

Many nutritional factors may operate in uteri (measured as the mother's exposure during pregnancy), and also during postnatal life, and the status of the child is often influenced both by the maternal intake during pregnancy and postnatal exposures. Because the most relevant timing of exposure and possible induction times are unknown for T1D, an approach addressing both intrauterine and postnatal exposure to hypothetical risk factors or protective factors is most sensible.

1.2.2 Breast-feeding and cow's milk

Several epidemiological studies indicate that the risk of T1D is lower in children that have been breast-fed compared to children given breast-milk substitute produced from cow's milk (Norris & Scott., 1996), and recent data also indicate that for avoiding early autoimmunity the duration of breastfeeding is of importance (Rosenbauer et al., 2008). But most case-control studies suffer from potential recall bias, and prospective studies up to now have been few and very small. Case-control studies have also found associations between cow's milk antibodies and T1D see e.g. (Sarugeri et al., 1999; Monetini et al., 2002), but some form of reverse causality cannot be excluded as alternative explanations for the association described in these studies. Although an early study indicated a role of so-called molecular mimicry between a protein in cow's milk and a β-cell antigen (Karjalainen et al., 1992), it was subsequently refuted (Rønningen et al., 1998). Multiple other biologically plausible mechanisms have also been proposed for the possible relation between short duration of breast-feeding or early introduction of cow's milk.

1.2.3 Introduction of solid food

Studies indicate that the time point for introduction of solid food, especially with regard to cereal products, may have an influence on the development of autoimmunity (Norris et al., 2003; Ziegler et al., 2003). Early exposure to cereals is against generally accepted recommendations on infant nutrition in all developed countries and occurs infrequently. For example, Scandinavian babies are rarely exposed to cereals before the age of 4 months. A prospective analysis of data from the Finnish Diabetes Prediction and Prevention (DIPP) study showed no relation between early or late introduction of cereals and emergence of advanced β-cell autoimmunity. Another study from Finland suggests that an early introduction of fruit, berries and roots associated independently with β-cell autoimmunity

(Virtanen et al., 2006). While a recent study found that higher maternal intake of potatoes in the last trimester of pregnancy was associated with delayed onset of autoimmunity in the offspring (Lamb et al., 2008). Inconsistencies between the studies indicate that additional studies are required, including resolving the question of what aspects of cereals or other solid food items which are involved.

1.2.4 Cod liver oil, vitamin D and omega-3 fatty acids

A Norwegian study found intake of cod liver oil by the mothers during pregnancy or possibly by the child during the first year of life to be associated with lower risk of T1D in the child (Stene et al., 2000), but a subsequent larger study indicated that the child's intake was most important (Stene & Joner, 2003). Other vitamin D supplements were not associated in the Norwegian studies, pointing towards a possible effect of long-chain omega-3 fatty acids. Such fatty acids (e.g. EPA, DHA) have anti-inflammatory effects and potentially preventive effects for T1D (Chase et al., 1979). Results from a case-control study indicated, however, that vitamin D supplementation in early childhood could protect against T1D , and this has also been supported both from an European collaborative study (EURODIAB, 1999) as well as in a prospective study of children born in 1965 in Finland (Hyppönen et al., 2001). The longitudinal, observational study, the Diabetes Study in the Young (DAISY), conducted in Denver, Colorado, between January 1994 and November 2006, suggested that higher consumption of total omega-3 fatty acids, which was reported by a food frequency questionnaire, was associated with a lower risk of autoimmunity in children at increased genetic risk for type 1 diabetes. This association was further sustained by the observation of a higher proportion of omega-3 fatty acids found in the erythrocyte membranes in a subset of the children. Given that fish are a source of both omega-3 fatty acids and vitamin D, vitamin D was initially included in the analysis, but no association was found (Norris et al., 2007). Neither was it support for an effect of marine omega-3 fatty acids analysed separately. Pilot data from the MIDIA study do, however, indicate a protective effect against progression from autoimmunity to development of T1D (unpublished data). Although epidemiological studies can suggest possible associations, randomized clinical trials are necessary to prove a cause and effect. The pilot trial Nutritional Intervention to Prevent (NIP) T1D among babies with high genetic risk was therefore recently initiated (Chase et al., 2009).

1.2.5 Vitamin E

Hypothesising that antioxidants may protect against destruction of β-cells, Finnish researchers measured serum α-tocopherol concentration in frozen sera from 19 cases who developed T1D and in about 60 individually matched controls from a prospective cohort of individuals aged above 20 years (Knekt et al., 1999). Higher α-tocopherol was associated with a significantly lower risk of T1D. Another study from Finland, attempted to replicate this finding in siblings of persons with T1D, and found partial support, although the results were not significant (Uusitalo et al., 2005). Recently both concentration of α- and γ-tocopherol were studied in the Type 1 Diabetes Prediction and Prevention project (DIPP). Although it seemed unlikely that high concentration of α- or γ-tocopherol protect against advanced β–cell autoimmunity in young children, there was a suggestive protective effect of high levels of γ-tocopherol at the age of 1 year on development of autoimmunity, which needs to be replicated (Uusitalo et al., 2008).

1.2.6 Sugar

A Norwegian study shows that children receive from 9% to 24% of their energy from added sugar in the diet, where a major part comes from soft drinks (Øverby et al., 2004). Despite the fact that the increase in intake of simple sugar (in the form of sweets and drinks) in ecological studies correlate with increasing incidence of T1D, only a couple of studies have attempted to investigate this at the individual level. In one study an association between sugar intake and T1D incidence was not found (Dahlquist et al., 1990), but in two more recent studies a correlation was found (Pundziute-Lycka et al., 2004; Benson et al., 2008). Both studies used a case-control design which is likely to suffer from recall bias. Prospective studies with proper registration of dietary habits are therefore needed. The role of diet at different ages in a child's life may also be important.

1.2.7 Overweight

A few studies have observed an association between high birth weight and increased risk of T1D (Stene et al., 2001), although the relation is not very strong, but overweight and obesity are increasing. Gestational diabetes in the mother is a risk factor for a high birth weight and gestational diabetes has increased the last decades. Today a considerable proportion of pregnant women have gestational diabetes. Gestational diabetes may be a consequence of increased body weight in connection with the increased insulin resistance following pregnancies in general. Data from the MIDIA study indicate that both the mothers Body Mass Index (BMI) before getting pregnant as well as high weight gain during pregnancy increase the risk for autoimmunity at an early age for the offspring (Rasmussen et al., 2009). Obesity during childhood is emerging as a possible risk factor for T1D (EURODIAB, 2002; Pundziute-Lycka et al., 2004), but further studies are needed, including to find what particular aspects of body size/obesity (such as inflammatory cytokines or other markers) are most relevant in this relation. Since all the potential relations described above have very important public health implications, the different factors need to be investigated in larger well-designed prospective studies.

1.3 The hygiene hypothesis

The hygiene hypothesis states that the lack of exposure to parasites, symbiotic organisms and infectious agents in early childhood increases the susceptibility to allergic and autoimmune diseases (Zazdanbakhsh et al., 2001). Since humans have evolved coexisting in a shared environment with microbial agents throughout much of our evolutionary history, these agents might be necessary for the development of a balanced and regulated immune system (Stoll, 1947). The decline in non-specific infectious and microbial exposure in many populations is thus proposed to be the cause of the concomitant increase in atopic disorder over the past few decades (Bachlin & Degremont, 1997), and this hypothesis has been extended to autoimmune diseases such as T1D (Kyronseppa, 1993).

1.3.1 The hygiene hypothesis and epidemiology

The hygiene hypothesis is supported by epidemiological studies that show higher prevalence of autoimmune diseases in North America and Europe compared to South America and Africa, higher incidence associated with increased material wealth and higher risk for autoimmune diseases for third world immigrants to the industrialized countries (Herrström et al., 2001). There are also many studies showing that some infections and microbial agents reduce the incidence of autoimmune diabetes in experimental animals

(Blaser, 1998; Malaty, 1994). There are fewer studies in man suggesting protective effect of childhood infections against T1D (Sepp et al., 1997; Samulsson & Ludvigsson, 2003; Horman et al., 2004).

1.3.2 Intestinal parasites

Since immunomodulatory effects of parasites have been reported (Samulsson & Ludvigsson, 2003), and there is evidence that infections protect against the development of allergic disorders, parasites become obvious and major candidates for the hygiene hypothesis. In 1947 it was reported that 40-60% of European children were positive for helminths (Horman et al., 2004), while in recent years only 5-23% are found positive (Strachan, 1989; Jones et al., 2000; Yazdanbakhsh et al., 2002; Cooke, 2009; Bach, 2002; Honeyman, 2005; van der Werf et al., 2007; Gibbon et al., 1997; Parslow et al., 2001; Pundziute-Lycka et al., 2003; Round & Mazmanian, 2009). The most prevalent of the helminths is Enterobius Vermicularis (pinworm) which is usually asymptomatic and each bout is self-limiting since the worms cannot reproduce within the gut. Most common of the water borne parasites are Cryptosporium and Giardia. While the genus Giardia comprises six species, more than 20 variants of Cryptosporium are known (Nygard et al., 2003).

1.3.3 Bacterial colonization and virus infection in the intestines

Another interesting possibility is that the age at infection makes a difference in the pathology. In a similar fashion, it has been shown that colonization of the gut and intestines in early infancy by bacteria plays a role in the development of the adaptive immune system and structural development of the gut (Strachan, 1989). It is well known that due to improved hygiene some viral infections that would normally occur in early life are encountered for the first time at a later stage. For example, mononucleosis is associated with late infection of Epstein-Barr virus (EBV) (Pohl, 2009). Mononucleosis is rare in third world countries. Similarly, hepatitis A and B are less likely to cause disease if exposed to at an early age, and chickenpox (caused by varicella-zoster virus) is more severe in adults. Apparently, late infections typically give rise to a more severe pathology and concomitant increased activation of the immune system. The increased activation of the immune system may dispose for the establishment of an autoimmune condition. This hypothesis would explain the apparent conflict in data indicating that viral infections may confer protection and susceptibility. The MIDIA study offers a unique possibility to test this hypothesis.

1.4 Viral infections as triggers of type 1 diabetes

Viral infections have long been considered as triggers of T1D, and there are several lines of evidence implying virus infections in utero or early life in the aetiology of T1D . The high frequency of T1D in children with congenital rubella syndrome was the first indication of a viral involvement, and hinted towards the importance of the intra-uterine environment (Menser et al., 1978). Intra-uterine rubella infection is now rare in Scandinavia due to vaccination, but the incidence of T1D is high and continues to rise. Mumps and measles were also suspected of playing a role in T1D (Vuorinen et al., 1992), and a plateau in T1D incidence in Finland was also noted after measles, mumps and rubella vaccine was introduced (Hyöty et al., 1993). Measles vaccination was also suggested to be protective in a Swedish study (Dahlquist et al., 1991). Another interesting observation is that acute viral infections can be associated with disease onset (Elfaitouri et al., 2007; Frisk et al., 1992; Osame et al., 2007). There is also a seasonal correlation between periods of viral infections

and onset of T1D (Jun & Yoon, 2003; Richer & Horwitz, 2003). Several viruses have been implicated as having an association with T1D, amongst them members of the picornaviridae and other viruses.

1.4.1 Mechanisms proposed for viral triggering of autoimmunity

There is unfortunately limited data on viral infections in young children (and infection load in early life), but there are several proposed mechanisms for how viruses might be associated with T1D. Viruses can activate polyclonal cells and trigger production of autoantibodies (Hiemstra et al., 2001), viruses can directly infect and lyse cells, viral antigens might mimic self-antigens, inflammatory responses stemming from viral infections might trigger autoimmunity (Horwitz et al., 1998), or as predicted in the hygiene hypothesis, viruses might be needed for proper maturation and regulation of the immune response.

1.4.2 Picornavirus

Picornaviruses are small RNA viruses that replicate mainly in the gut, and are spread by the fecal-oral route. The family has several well-known human and animal pathogens, but also many viruses without any known pathology. Human picornaviruses are known to be mostly asymptomatic and are common in infancy, with a prevalence of 10-12% in stool samples for human enterovirus (Cinek et al., 2006), human parechovirus (Tapia et al., 2008) and cardiovirus (Blinkova et al., 2009). The picornaviridae family currently consists of 8 current genera and 4 proposed genera.

The enterovirus genus consists of ten species, with six of them having human hosts (human enteroviruses A-D, rhinovirus A-B). Human enteroviruses are the most promising candidates, with two case-control studies that have shown an association between maternal enterovirus infection during pregnancy or enterovirus infection in children and risk of T1D (Dahlquist et al., 1995; Viskari et al., 2005). There are also studies that showed no association (Richer & Horwitz, 2009). In particular, Coxsackievirus (a member of human enterovirus B) is suspected of having a role in the development of autoimmunity (reviewed in Graves et al., 2003). In addition, enteroviruses have been shown to be more present in the sera (Elfving et al., 2008; Oikarinen et al., 2008), small intestine (Richardson et al., 2009) and pancreatic islets (Harvala & Simmonds, 2009) of recently diagnosed T1D patients (Clements et al., 1995; Andreoletti et al., 1997). A recent study by our group suggest that there is less enterovirus infections among children with high genetic risk for T1D compared with control children, although the difference is not statistically significant due to the low number of children presently tested (Tapia et al., 2011). Moreover, there appear to be a higher prevalence of enterovirus infections during early life in children who do not develop autoimmunity later, suggesting that enteroviral infections confer a protective effect against the development of autoimmunity (Wolthers et al., 2008). The parechovirus genus consists of two species, the murine virus Ljungan virus (LV) and human parechovirus (HPeV). Human parechovirus 1 and 2 have been known since the 1960s, and were originally classified with the enteroviruses as echovirus 22 and 23. Several new parechoviruses have recently been reported, with HPeV3-8 being described from 2004 to 2009 and HPeV9-14 recently announced. They are common in children, uncommon in adults and are present worldwide. Our previous data show that human parechoviruses are present in approximately 12% of stool samples from infants without causing symptoms (Tapia et al., 2008). There are, however, studies linking them to several serious conditions. Our most recent case-control

study shows no difference in positivity for human parechovirus infections in stool samples (Tapia et al., 2010). Ljungan virus has earlier been shown to cause diabetes-like condition in rodents (Niklasson et al., 2006), but was not identified in samples from children in our studies (Tapia et al., 2008, Tapia et al., 2010). HPeV1 has been reported to show no association with T1D (Tauriainen et al., 2007), but there is no data on the other types of HPeVs. However, sequencing should be done to see if there is any difference in strains, and to test for all the new human Parechoviruses. Human parechoviruses seem to be asymptomatic, common viruses in childhood, and data on their epidemiology (and of other common asymptomatic viruses) will be used to test the hygiene hypothesis.

1.4.3 Cardiovirus

The genus Cardiovirus consists of 2 species, encephalomyocarditis virus and theliovirus (Liang et al., 2008). Until recently only rodent cardioviruses have been known. Encephalomyocarditis virus has been shown to induce diabetes in mice, and thelioviruses have been associated with myocarditis, and MS like symptoms in mice (Chiu et al., 2008). Recently, human thelioviruses, termed Saffold virus 1-8, have been discovered (Drexler et al., 2008). There is little known about them, but a serological study shows that SAFV3 are ubiquitous and cause infection early in life (Zoll et al., 2009), but are apparently asymptomatic. Being a recently discovered virus, only a few studies have detected it with molecular methods (Abed & Boivin, 2008; Jones et al., 2007; Day, 2009; Coulson et al., 2002), so making assumptions about its epidemiology may be premature. Being in the picornaviridae family, and being closely related to rodent pathogens suggest they might be unknown human pathogens, and they should be studied both to get a clear picture of infections in early childhood and if there is any association with T1D in humans. The MIDIA study offers an excellent opportunity to study these viruses.

1.4.4 Reovirus

The family reovirus consists of six genera. Two of these genera, rotavirus and reovirus, have been shown to infect β-cells, and are of interest to the project. They are double-stranded RNA viruses, also known to be common and ubiquitous (Honeyman et al., 1998). Rotaviruses are the single most important cause of severe diarrheal illness in infancy in both the developed and undeveloped world. They are spread through the fecal-oral route. Studies in mice have shown infection of β-cells (Comins et al., 2008) indicating molecular mimicry (Toniolo et al., 1980). These viruses are being studied by a post doc. in the MIDIA project, and we will pool our data to study the infections in childhood.

The name reovirus is a derivation of respiratory enteric orphan viruses, acknowledging that they can infect the respiratory and gastrointestinal system, but are not associated with any known disease (Wetzel et al., 2006). They are generally regarded as benign, but have also been associated with symptoms. In mice, they have been shown to infect β-cells, but have also been shown to delay overt diabetes in mice. Screening longitudinally collected stool samples for these viruses will show whether they are associated with any disease in human infants, and also be used to test the hygiene hypothesis.

1.4.5 Other viruses

Our results show that infections in early life are much more prevalent and asymptomatic than previously known, but also highlight the need for more studies on viral infections in

children. There are several viruses that are considered common in childhood that should be studied to test the hygiene hypothesis, and viruses that have been implicated with T1D, or human strains of animal viruses associated with T1D, should be studied. In addition, newly discovered viruses will also be evaluated as candidates for testing. However, these viruses will have a lower priority than the candidates listed above.

1.5 Psychosocial effects of risk information

We are all born with variants in our genes which make us susceptible to diseases. With the developments in biotechnology and increasing knowledge about the relation between genes and diseases, we are faced with both new opportunities and new dilemmas. The use of tests that provide knowledge about risks and possibilities for illness in the future raises many fundamental questions of ethical, legal and psychosocial character.

1.5.1 Cohort studies giving risk information

In the MIDIA study parents were informed about that their child had the high-risk genotype for T1D (babies carrying HLA-DRB1*03-DQA1*05-DQB1*02/ DRB1*04:01-DQA1*03-DQB1*0302) or not. 2.1% of Norwegian newborns carry the high-risk genotype, and this group represents approximately 34% of future cases of T1D. Children with the high-risk genotype have 7% risk for getting T1D before 15 years of age and a lifetime risk at 20% (Rønningen et al., 1991; Undlien et al., 1997; Joner & Søvik, 1982, 1989; Mølbak et al., 1994).
Several other studies have used predictive genetic testing of newborns as a strategy to solve research questions about environmental factors contributing to T1D, including BABYDIAB in Germany (Ziegler et al.; 2011, Schatz et al.; 2000), DIPP in Finland (Kimpimaki et al.; 2001), PANDA in Florida (Carmichael et al., 2003, Krischer, 2007), DiPiS in Sweden (Lernmark et al., 2004), DAISY in Colorado (Rewers et al., 1996), and the multinational TEDDY study in the USA and Europe (Kiviniemi et al.; 2007, TEDDY study group; 2008). The main advantage for study participants identified as having increased risk for T1D is the possibility of early detection of the destruction of the insulin producing cells by autoantibodies, resulting in a milder disease onset having parents who are prepared in advance for the possibility of T1D onset, and therefore will handle the new life situation with a child with T1D better than other parents. In addition children with known increased genetic risk for T1D who also have developed autoantibodies will be the first to participate in intervention studies when possible preventive get available. However, there may be disadvantages of living with the knowledge of an increased susceptibility to a disease with no prevention. Thus, even though predictive testing is highly acknowledged as a valuable research method per se, the predictive testing has given rise to concerned debate.

1.5.2 Particular aspects for the Norwegian MIDIA and MoBa studies

With the widespread and increasing use of genetic tests, assessing the adverse effects of information about susceptibility genes for disease on the tested subject is important. The MIDIA study aimed to estimate the effect on maternal mental health from receiving genetic risk information about their newborns. Outcome measurements were maternal self-reported scores of anxiety and depression symptoms, satisfactory with life, self-esteem, and serious worry about their child. A number of previous studies (Hood et al., 2005; Johnson et al., 2004; Kerrush et al., 2007) have examined maternal reactions after being informed about their children having elevated genetic risk for T1D. None of these studies have shown a

significant effect on symptoms of anxiety or other mental health disorders as result of the testing, though a few mothers did seem to react strongly. Previous studies were conducted in a setting in which the mothers were asked questions about it in connection with the genetic testing project. The MIDIA study was designed differently. When completing the questionnaire the mothers were not aware that their answers were going to be used for any particular comparisons, though they were rightfully informed that the personal data would be used for multiple research purposes. Thus, our results were not affected by reporting bias associated with maternal attitudes towards genetic risk information or other factors motivating to under- or over-report poor mental health. Since 50% of mothers who got their child tested for genetic high-risk for T1D also participated in the Norwegian Mother and Child Cohort (MoBa) study, all data used came from MoBa. In MoBa data was available both from the 30th week of pregnancy and when the child was 6 months of age. These data therefore permit to answer the main question to what extent receiving information about a young child having high risk for T1D changes maternal well being and health.

2. Material and methods

2.1 Research design and subjects

The MIDIA study is a longitudinal cohort study with inclusion of children with the high-risk HLA genotype (DRB1*04:01-DQA1*03-DQB1*03:02/DRB1*03-DQA1*05-DQB1*02), with follow-up from three months of age up to 15 years of age. Recruitment to MIDIA started in small scale in the summer of 2001, covered the whole country of Norway from March 2006 (60,000 births per year) and was stopped in December 2007 since it was suddenly found to be against the Norwegian Biotechnology Law. Both approvals from the Regional Medical Committee and the Norwegian Data Inspectorate had been given before recruitment to MIDIA started. In December 2007 close to 48,000 children were recruited to MIDIA. Of those 1,047 were identified with the high-risk genotype. Approval from the government was given for further follow-up of those already identified with the high-risk genotype. At the end of March 2011, 19 of these children had got Type 1 Diabetes, 33 were confirmed positive for two or three autoantibodies and 24 for one. A total of 4,829 blood samples, 18,275 stool samples and 4,412 questionnaires are presently available for analysis in the cohort.

A questionnaire summarizing weekly diaries was filled out at 3, 6, 9 and 12 months of age. Blood samples were taken at the same intervals. After this period, a questionnaire and a blood sample are asked for annually (Stene et al., 2007). For more information on MIDIA, see www.fhi.no/midia. In The Norwegian Mother and Child Cohort Study (MoBa), questionnaires have been asked for at 17th, 22nd and 30th week of pregnancy, and when the child is 6 and 18 months old as well as then the child get 3, 5, 7 years of age (Magnus et al., 2006) . Blood samples were asked for at 17th week of pregnancy and at the time of delivery from the mother and cord blood was taken from the baby (Rønningen et al., 2006). For more information on MoBa, see www.fhi.no/morogbarn.

2.2 Outcome measurements

The incoming blood samples in the MIDIA study are immediately tested at the Hormone Laboratory, Aker Hospital, for diabetes associated autoantibodies as marker of β-cell autoimmunity, autoantibodies against insulin, anti-glutamic acid decarboxylase (GAD), and against the protein tyrosine kinase related protein IA-2 (Petersen et al., 1994; Bingley et al., 2001). High titres of one autoantibody or titres above the cut-off for two or three

autoantibodies on at least two consecutive time periods (3-6 months apart) is defined as islet autoimmunity for the purpose of data analysis, and will be used as the first outcome (optimal cut-off values for the autoantibodies has been defined after participation by the Hormone laboratory in international autoantibody standardisation workshops; DASPs). Clinical diagnosis of T1D will also be used as outcome, and analysis will be performed when a sufficient number of children have developed either autoimmunity or T1D.

2.3 Measurement of nutrition-related factors ("exposures")

2.3.1 Questionnaires

A questionnaire summarising weekly diaries were filled out when the children were 3, 6, 9 and 12 months old, and annually thereafter. The questionnaires include for examples detailed information about dietary habits of the mother and the child (detailed information about diet for the mother as long as she breast-fed and intake of specific food items, etc.). Since few studies have been conducted on children's diet in Norway, new dietary questions had to be developed for both the MIDIA and the MoBa study. Validation of various aspects of dietary habits of pregnant women has recently been undertaken within the MoBa study. Blood samples and questionnaires from MIDIA can be used to assess validity of relevant information in childhood (Brantsæter et al., 2007a, 2007b, 2008, 2009; Willett, 1998; Serdula et al., 2001).

2.3.2 Biomarkers: Fatty acids, vitamin D and E

The distribution of fatty acids in the plasma phospholipid fraction as well as Vit D and Vit E will be analyzed in plasma samples from the same aliquots at a commercial laboratory in Oslo (AS Vitas; http://www.vitas.no/) using solid phase extraction and gas chromatography.

2.4 Measurement of exposure to virus (viral infections)

2.4.1 Real-time PCR

The real-time PCR have been run on ABI7300 real times machines according to earlier publications (Cinek et al., 2006). Primers were first designed for main type of virus and thereafter for subtypes (serotypes) and optimalisation was performed for each of the reactions.

2.4.2 Sequencing

Sequencing for enterovirus, picornavirus and E.coli as well as other bacterial species will be done as earlier published (Tapia et al., 2011; Witsø et al., 2006, 2007; Muinck et al., 2011). Deep sequencing will be performed on at 454 machines at the Centre for Ethological and Evolutional Sciences (CEES), Institute of Biology, University of Oslo according to the manufacture instructions.

2.4.3 Questionnaires

Data from questionnaires will be used to test association between viral RNA/DNA in stool and symptoms reported by the parents (coughing, diarrhea, vomiting), and will be used to search for risk factors of viral infection, such as breastfeeding, number of siblings and socioeconomic status.

2.5 Identification of eggs from enterobius vermicularis

Parents of children participating in MIDIA have been asked to collect tape samples touching the anal region on three following mornings. They have then sent the samples in specially designed containers for tape sampling to the central laboratory in Oslo. Here all the tape samples have been examined by two scientists at different times. A child has been regarded as positive if down to one egg have been identified on one of the tapes.

3. Results

3.1 Psychosocial effects of risk information

3.1.1 Effects of genetic risk information on mental health variables among MIDIA mothers

In the study of mothers who had participated in both MIDIA and MoBa (N=166 for those having a child with high genetic risk for T1D and N=7,224 for those who had been told that their child did not have the high-risk genotype) there were no sosiodemographic characteristics differences between those who had got the risk-information and those who had let their child be genotyped in MIDIA, but had been told that their child did not carry the high-risk genotype. Information on genetic risk in newborns was found to have no significant impact on maternal symptoms of anxiety and depression, self-esteem, satisfaction with life, or serious worry about their child. Mental health before birth was strongly associated with mental health after birth, see Table 1. Maternal symptoms of anxiety and depression were assed using a short version of SCL-25, including 4 question for anxiety and 4 for depression (Aas et al., 2010). The five-item Satisfaction With Life (SWLS) was developed to measure the cognitive component of subjective well-being. The short-form of the Rosenberg Self-Esteem Scale (RSES) used in the MoBa study includes four items. Maternal worry about their child was one of the items in an 11-item checklist of life events experienced during the last year, given in the 6 month questionnaire. The question was phased "Have you been serious worried that there is something wrong with your child?" Responses were coded as "yes" or "no". A dichotous variable was constructed to indicate the presence of maternal T1D. The variable was based on health questions from both The Medical Birth Registry of Norway (MBRN) and the MoBa questionnaires. The results from the linear regression analyses of the association between genetic risk information and change in maternal mental health are shown as unstandardized (B) and standard (β) coefficients in Table 1. The upper part of the table shows the results from the regression analysis with symptoms of anxiety and depression (SCL) as the dependent variable. The estimated regression coefficient (B=-0.001, p=0.95) for child's genetic risk indicate no effect of genetic information on changes in maternal mental health from baseline to post-disclosure. The maternal T1D status had neither any effect (B=0.040, p=0.409). However, as expected, the baseline anxiety/depression score was strongly associated with post-disclosure scores (B=0.536, $p<0.001$).

3.1.2 How often do parents think on that they have a child with high genetic risk for T1D

Although 5% of mothers and 2% of fathers did think of their child's high genetic risk for T1D when they filled out the 3 month questionnaire, usually just 2 week after they had got the information, very few parents continued to think often about their child's high genetic risk for T1D. To answer the questionnaire with the same questions each time needs that you sometimes think about having a high-risk child for T1D, see Figure 1 and 2.

Effects of maternal diabetes and genetic risk information on mental health variables

	B (95% CI)	β	p	Adjusted R^2
Symptoms of anxiety and depression				
Child's genetic risk	-0.001 (-0.047 - 0.044)	-0.001	0.953	
Maternal type 1 diabetes	0.040 (-0.055 - 0.135)	0.008	0.409	
Baseline anxiety/depression	0.536 (0.517 - 0.555)	0.544	< 0.001	
				0.296
Self esteem				
Child's genetic risk	0.037 (-0.022 - 0.097)	0.011	0.218	
Maternal type 1 diabetes	-0.040 (-0.164 - 0.083)	-0.006	0.521	
Baseline self esteem	0.682 (0.664 - 0.700)	0.651	< 0.001	
				0.423
Satisfaction with life scale				
Child's genetic risk	-0.080 (-0.198 - 0.039)	-0.013	0.187	
Maternal type 1 diabetes	0.016 (-0.231 - 0.263)	0.001	0.902	
Baseline SWLS	0.609 (0.590 - 0.628)	0.587	< 0.001	
				0.345

Table 1.

3.2 Nutrition-related factors

Cohort design was used for assessing whether BMI before pregnancy and weight gain during pregnancy predicted the risk of islet autoimmunity in 885 children who were followed with serial blood samples and questionnaires. 36 of the children developed autoimmunity, of whom 10 developed Type 1 Diabetes. Both maternal BMI before pregnancy and weight gain < or = 15 kg predicted increased risk for islet autoimmunity, significant hazard ratio at 2.5 for both situations (Rasmussen et al., 2009).

3.3 Virus in stool samples

Among 911 children, were stool samples were available, 27 had developed autoimmunity in two or more consecutive samples (case children) in December 2008. In the pilot study based on these cases two control children per case were matched by follow-up time, day of birth, and county of residence. The frequency of human enterovirus RNA in stool samples from cases before seroconversion (43 of 339, 12.7%) did not differ from the frequency in control subjects (94 of 692, 13.2%) (Tapia et al., 2011a). There was neither any difference in the prevalence of human parechovirus when cases and controls were compared: 13.0% and 11.1%, respectively (Tapia et al., 2011b). None of the 3,803 samples analysed were positive for rodent parechovirus-Ljungan virus (Tapia et al., 2008, Tapia et al., 2010). Indicating that Ljungan virus is rare among Norwegian children, and in contract to what have been reported earlier does not seem to be involved in T1D susceptibility.

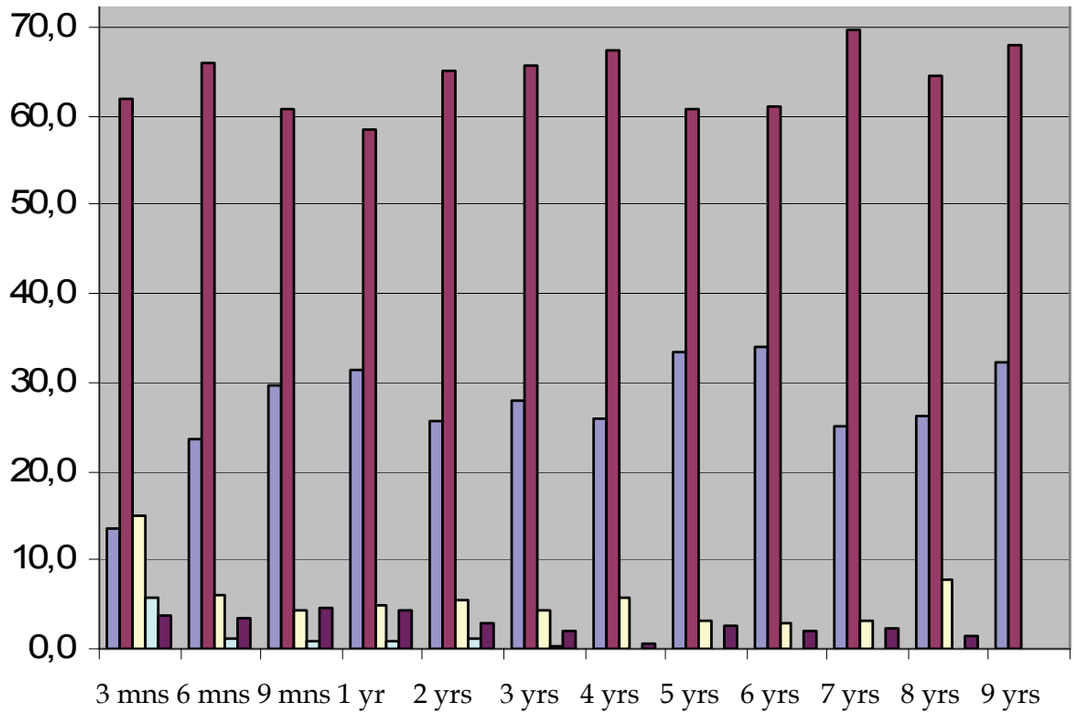

Fig. 1. Mothers thoughts about having a child with high genetic risk of T1D

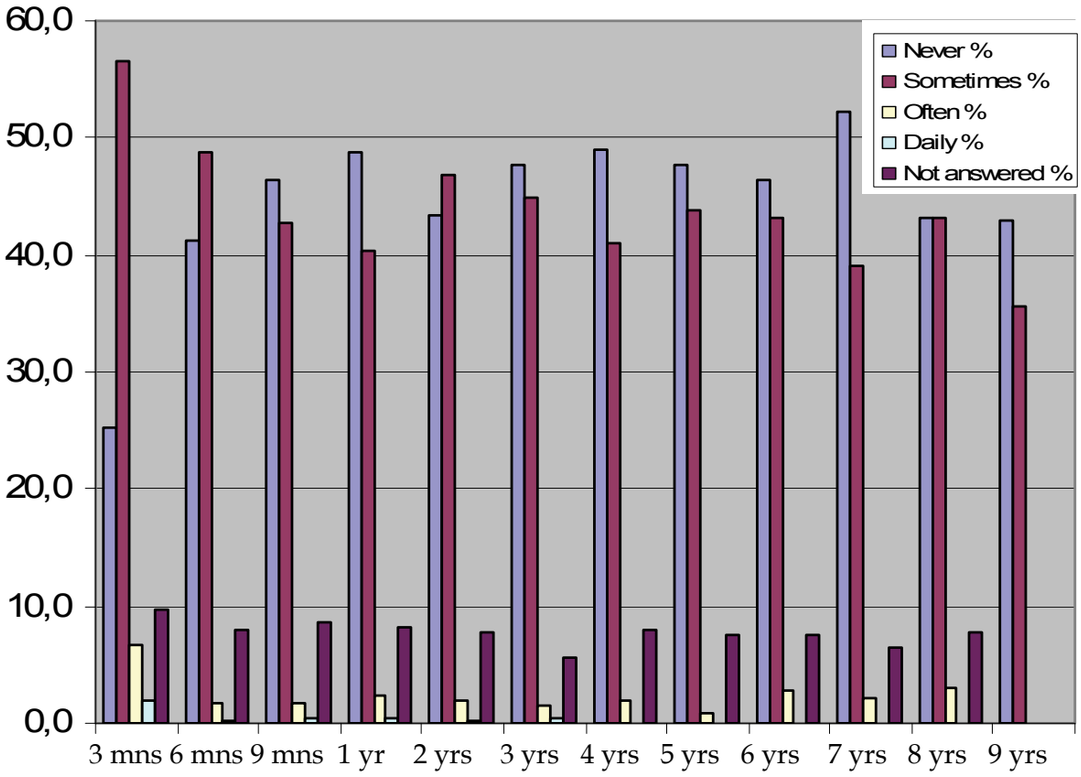

Fig. 2. Fathers thoughts about having a child with high genetic risk of T1D

3.4 The frequency of enterobius vermicularis among MIDIA children

During the last generation T1D has shown a strong increase in incidence in the Western part of the world. During the same period also the number of children suffering of allergic diseases has increased. In countries in Africa both T1D and allergic diseases are rare. The aim of this study was to examine if this had to do with the decrease in children having enterobius vermicularis (pinworm). Data has shown that intestinal worms are involved in development of intestinal immunity. The prevalence of pinworm has decreased in all European countries. While 40-60% was infected in 1947, only 5-23% has been shown positive in recent reports (Herrström et al., 1997). In MIDIA all who still participated in the project (N=943), was in the period January-June in 2010 invited to send in anal tape samples taken 3 following mornings. Of the 397 who participated, 18% did have pinworm egg on at least one of the tapes. This was a much higher frequency than expected, but more analysis will be performed, including analysis of the particular questionnaires developed for this project.

3.5 Lower respiratory tract infections

A MIDIA cohort study was most recently able to study 42 cases and 843 non-cases, which showed that self-reported "pneumonia, bronchitis or RS-virus" gave a hazard ration at 3.5, p=0.001 for developing for islet autoimmunity before 4 years of age.

4. Discussion

4.1 Data from the MIDIA project

The first nested case-control study in MIDIA on intestinal virus as triggers for Type 1 Diabetes did not support the hypothesis that faecal shedding of enteroviral RNA is a major predictor of advanced islet autoimmunity. Neither was there any association between human parechovirus and islet autoimmunity. Although also the rodent parechovirus, Ljungan virus, has been proposed as a potential environmental trigger for Type 1 Diabetes, the results from the MIDIA study indicate that Ljungan virus is rare in young children since it was not found neither in controls or cases. The two cohort studies performed in MIDIA do, however, show that both maternal weight and self reported lower respiratory tract infections predict risk of islet autoimmunity, and particularly in the youngest age group. The MIDIA study did not find any evidence supporting the notion that genetic risk information about newborns has a negative impact on the mental health of Norwegian mothers. All recruitment to the MIDIA study had, however, to be stopped in December 2007. The following part of the discussion will focus on the reason and the consequences for further research on environmental triggers of T1D.

4.1.1 Stopping of an ongoing T1D study based on the Norwegian Biotechnology Law

The MIDIA study had the needed approvals for research studies in Norway (from the Regional Ethic Committee and the Data Inspectorate) before recruitment started in the summer of 2001. Since all recruitment was based on special teaching of Norwegian public health care nurses given by the principal investigator and a study coordinator, the recruitment started in small scale. Most of the public health care nurses in Norway started after they had got the needed information and education to voluntary recruit to MIDIA as well as being responsible for most of the blood samples taken. From 2006 the recruitment covered the whole country. In June 2007, one of the mothers of a participating baby was, however, interviewed in the biggest newspaper in Norway. She here complained about not

haven received good enough information about MIDIA before she and her husband had consented to participate. The Directorate for Health and Social Affairs then immediately decided that recruitment to MIDIA had to be stopped. Some days later it was, however, decided that new evaluation of the project had to take place according to the Norwegian Biotechnology Law, which tells that genotyping of children under the age of 18 years can only take place if there are a clear health benefit for a certain disease to get knowledge about genetics. During the fall of 2007 both the Biotechnology Board, the Ethical Committee for the Norwegian Medical Association, the National Committee for Medical Ethics as well as several experts contacted by the Directorate of Social and Health Affairs evaluated the MIDIA project. All these boards had earlier evaluated the MIDIA study; e.g. during the time of recruitment to the study. In addition the Health Department had clearly told that children who also had developed autoantibodies in MIDIA could get health insurance. The last aspect was based on the Biotechnology Law, which Norway has had since 1994, where it is clearly told that genetic risk for a disease cannot be used by the health insurance companies. The Directorate of Social and Health Affairs found, however, genotyping in MIDIA illegal December 10, 2007. A few days after the Norwegian Data Inspectorate said in newspapers that all data already collected from participants in MIDIA had to be thrown away. All ended luckily up with voting in the Norwegian Parliament in June 2008. As long as the Medical Regional Committee and the Norwegian Data Inspectorate approved the MIDIA study ones more, and all parents of children who already had been identified as high-risk children, gave a new informed consent , research in MIDIA could continue. In this respect Norway is different from Sweden, Finland, Germany and five states in USA were no similar Biotechnology Law Has given problems with genotyping of 350,000 children for the TEDDY study.

4.1.2 Ethics and data protection in human biomarker studies

The Norwegian Biotechnology Law tells: "Genetic testing of a child under the age of 18 years is not allowed if circumstances cannot be detected that can reduce or prevent health disadvantages for the child." Since the law came in 1994 it had only counted for clinical practice, the MIDIA project had been run for 6 ½ year before it was stopped December 10, 2007. In the work performed before the law got in use, science was never mentioned. Important questions in this context are:

1. Do important scientific T1D projects involving genotyping of children have to be performed elsewhere in the word? Should not Norway as one of the riches countries in the word has a certain responsibility?
2. Are not the parents able to give informed consent of behalf of their child?
3. How should health benefit be defined?
4. Is it not so that if clear health benefit has been shown, it is no longer research but part of general recommendation for public health or part of the health care system?

The year after recruitment to MIDIA was stopped funding was given from the Norwegian Research Council to the study "Nutritional Intervention to Prevent Type 1 Diabetes". The project was based on that the incidence of T1D is increasing, particularly in very young children. The hypothesis was that the Decrease of omega-3 fatty acids in the diet has contributed to this increase. One case-control study from Norway reported that children with T1D less often than the control children had a mother who had taken cod liver oil during pregnancy, while a newer study from Norway indicated a protective effect of cod liver oil during infancy (Stene et al., 2000; Stene & Joner, 2003). In the longitudinal, observational study, the Diabetes Autoimmunity Study in the Young (DAISY), conducted in

Denver, Colorado, between January 1994 and November 2006, 1770 children at increased genetic risk were followed. Islet autoimmunity was assessed in association with reported daily intake of polyunsaturated fatty acids. The data strongly indicated that dietary intake of omega-3 fatty acids is associated with reduced risk for autoimmunity in children at increased risk for T1D (Norris et al., 2007). We therefore proposed to conduct a prospective double blinded dietary intervention trial using high dosage of the omega-3 fatty acid DHA or "placebo" (containing the same amount of DHA found in the recommended daily dosage of cod liver oil). The reason for choosing 1,8 g DHA daily was to be able to be included in a multi-centre study since a pilot study in USA already have been performed as a feasibility study using exactly this dosage. But in USA they use plant oil as placebo (Chase et al, 2009). In Norway this cannot be given since mother of babies in Norway get recommended from their public health care nurse to give cod liver oil. But they are told to start with one tea spoon and to increase the daily intake to 5 ml within the child is 6 months. But at this stage babies start spotting. Indeed very few parents continue to give their infant cod liver oil. The Directorate for Health decided, however, that "Nutritional Intervention to Prevent Type 1 Diabetes" was illegal, and could therefore never be started based on the Norwegian Biotechnology Law.

4.1.3 Need for trans-national studies

Most recently two big NIH funded studies are going on. In the Type 1 Diabetes Genomics Consortium forces worldwide have been working together. All genotyping has been based on linkage studies (two siblings with Type 1 diabetes and parents without the disease is needed). Getting all who earlier was competing in identifying new T1D susceptibility genes to collaborate gave access to all available multiplex families. All genes that earlier was indicated to be of importance for T1D were confirmed, and 40 genes conferring susceptibility to T1D has now been identified (Barrett et al, 2009). In addition genome wide association studies have been performed by the same group (Welcome Trust Case Control Consortium, 2010).

In TEDDY (The Environmental Determinants for Type 1 Diabetes in the Young), another NIH funded study, centres in Denver, Colorado, Seattle, Washington, parts of Georgia and Florida, parts of Finland, Sweden and Germany have recruited and genotyped 350,000 new-borns and inform the parents about the high genetic risk. The protocol is the same everywhere, and all collected samples are sent to the coordinating centre in Florida. The follow-up is more intense than in MIDIA. Here all who participate, both scientists and parents know that it is an observational study where any intervention never can be given. The children Will be followed-up for 15 years.

5. Conclusions

The first nested case-control study in MIDIA on intestinal virus as triggers for Type 1 Diabetes did not support the hypothesis that faecal shedding of enteroviral RNA is a major predictor of advanced islet autoimmunity. Neither was there any association between human parechovirus and islet autoimmunity. Although also the rodent parechovirus, Ljungan virus, has been proposed as a potential environmental factor for Type 1 Diabetes, the results from the MIDIA study indicate that Ljungan virus is rare in young children since it was not found neither in controls or cases. The two cohort studies performed in MIDIA do, however, show that both maternal weight and self reported lower respiratory tract

infections predict risk of islet autoimmunity, and particularly in the youngest age group. The MIDIA study did not find any evidence supporting the notion that genetic risk information about newborns has a negative impact on the mental health of Norwegian Mothers. Recruitment to MIDIA was stopped based on the Norwegian Biotechnology Law. It is therefore needed to extend international collaboration to identify the environmental triggers of type 1 diabetes. With the estimated increase of children with 50% having Type 1 Diabetes in 2020, and that the increase will be highest among children younger than 5 years (increase in prevalence with 70%) it is really important to extend collaborative efforts.

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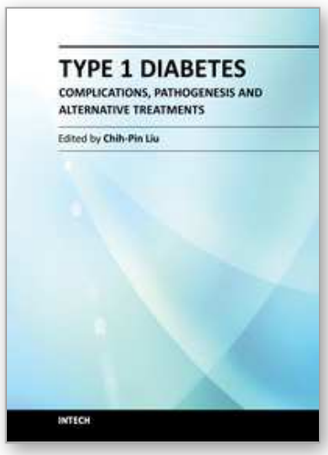

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This book is intended as an overview of recent progress in type 1 diabetes research worldwide, with a focus on different research areas relevant to this disease. These include: diabetes mellitus and complications, psychological aspects of diabetes, perspectives of diabetes pathogenesis, identification and monitoring of diabetes mellitus, and alternative treatments for diabetes. In preparing this book, leading investigators from several countries in these five different categories were invited to contribute a chapter to this book. We have striven for a coherent presentation of concepts based on experiments and observation from the authors own research and from existing published reports. Therefore, the materials presented in this book are expected to be up to date in each research area. While there is no doubt that this book may have omitted some important findings in diabetes field, we hope the information included in this book will be useful for both basic science and clinical investigators. We also hope that diabetes patients and their family will benefit from reading the chapters in this book.

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