Diabetes Mellitus and Oral Health

AN INTERPROFESSIONAL APPROACH

Edited by Ira B. Lamster



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To my wife Gail, and our children and grandchildren, for the love and balance they provide.

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Introduction

Diabetes mellitus is a group of endocrine disorders characterized by elevated levels of glucose in blood. The underlying cause is either an absence of insulin production, a lack of responsiveness to the actions of insulin, or some combination of both. The direct and indirect consequences of diabetes are enormous, resulting in significant morbidity and mortality. Diabetes is a chronic disease, and patients are required to manage their disease for decades. This reality can have a major impact on a person's lifestyle, and achieving the normal range of blood sugar in blood requires daily vigilance.

The financial cost of caring for patients with diabetes mellitus in the United States is estimated to be nearly a quarter of a trillion dollars per year [1]. Furthermore, the personal toll on patients and their families is enormous. Complications of the disease include vision problems leading to blindness, end-stage renal disease requiring kidney transplantation, increased incidence of myocardial infarction and strokes, and poor wound healing resulting in amputation.

Diabetes mellitus is of particular importance for dental professionals:

- The prevalence of diabetes is increasing. Based on data from 2011 [2], 25.8 million people in the United States have diabetes, representing 8.3% of the population. Furthermore, now there is interest in prediabetes, a condition in which the blood glucose level is above normal but not elevated enough to be classified as diabetes. Individuals with prediabetes are at risk for development of type 2 diabetes mellitus and its complications. It is estimated that more than 80 million adults in the United States have prediabetes [2]. Consequently, patients with dysglycemia are now, and will in the future, routinely be seen in dental offices.
- Older individuals in the United States and other developed countries are retaining their teeth, and in the future will require more dental services.
- There are a number of important oral manifestations of diabetes mellitus, including greater severity of periodontal disease, increased root caries, xerostomia, candidiasis, burning mouth syndrome, and benign parotid hypertrophy. Diabetes mellitus is the only systemic disease that is a recognized risk factor for periodontitis [3]. Because more than 25% of people with diabetes are unaware that they are affected [2], a person with undiagnosed diabetes may present to the dental office with an oral manifestation of the disease. Furthermore, because oral manifestations of diabetes are more common with poor metabolic control, an oral manifestation of diabetes may be an indication of a patient who requires medical attention to better manage his or her disease.

- There is mounting evidence that advanced periodontitis can adversely affect metabolic control in patients with diabetes [3]. Periodontal therapy provided to patients with periodontitis and diabetes has resulted in a significant decrease in the level of glycated hemoglobin.

As dental professionals consider the future of dental practice, and with the realization that an increasing number of patients with chronic diseases requiring multiple medications will be seen for dental care, an understanding of the etiology, prevalence, management, and clinical complications, including the oral complications of diabetes, is essential. This book will address this need, and is divided into three sections. There are four chapters in the medical considerations section, including (1) etiology, (2) epidemiology, classification, risk factors, and diagnosis, (3) medical complications, and (4) treatment. There are five chapters in the dental considerations section, including (5) management of the patients with diabetes in the dental office, (6) periodontal complications of diabetes, (7) the influence of periodontal disease on metabolic control, (8) non-periodontal oral complications of diabetes, and (9) assessment of diabetes mellitus in the dental office. The final section presents six case scenarios which describe patients with diabetes who are seen in the dental office, and illustrates how management of each requires dental professionals to have a thorough understanding of diabetes mellitus and work closely with other health care providers to deliver the most appropriate care. Furthermore, medical professionals must understand the importance of the oral cavity in the context of diabetes, identify oral problems when present, and refer patients for routine care.

Finally, this book is also notable because it makes a strong case for complete dental care being dependent upon an understanding of the entire patient. Dental care for medically complex patients demands that health care providers cooperate, and diabetes provides an excellent example of the importance of interprofessional practice. The result will be improved oral health, and health, outcomes. The results will benefit both patients and providers.

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Section 1
Medical considerations

Chapter 1

Etiology of diabetes mellitus

Ravichandran Ramasamy, PhD
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Introduction

The defining characteristics of diabetes, irrespective of the precise etiology, relate to the presence of hyperglycemia. The American Diabetes Association (ADA) has set forth specific criteria for the definition of diabetes. In the ADA guidelines, the following are necessary for the diagnosis of diabetes: (1) hemoglobin A1c (HbA1c) equal to or greater than 6.5% OR (2) fasting plasma glucose equal to or greater than 126 mg/dl OR (3) two-hour plasma glucose equal to or greater than 200 mg/dl during an oral glucose tolerance test (OGTT) (glucose load containing 75 grams anhydrous glucose dissolved in water) OR (4) in a patient with classic symptoms of diabetes or during a hyperglycemic crisis, a random glucose of equal to or greater than 200 mg/dl suffices to diagnose diabetes [1].

In this chapter, we will review the major types of diabetes and the etiologic factors that are known to or are speculated to contribute to these disorders. Furthermore, we will take the opportunity to present an overview of emerging theories underlying the pathogenesis of type 1 and type 2 diabetes. Types 1 and 2 diabetes constitute the vast majority of diabetes cases. Interestingly, both of these types of diabetes are on the rise worldwide [2, 3]. In addition to types 1 and 2 diabetes, we will also discuss gestational diabetes. Often a harbinger to the ultimate development of frank type 2 diabetes in the mother, this form of diabetes is potentially dangerous to both the mother and the developing fetus. Finally, we will discuss the syndromes known as MODY or maturity onset diabetes of the young. The disorders underlying MODY have very strong genetic components and are due to mutations in multiple distinct genes.

The greatest long-term danger of diabetes, irrespective of the etiology, lies in the potential for complications. The complications of the disease are insidious, deadly, and difficult to treat or reverse; hence, there is great urgency to identify specific means to prevent or mitigate these most common types of diabetes.

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Type 1 diabetes

Type 1 diabetes accounts for approximately 5–10% of all cases of diabetes [1]. The countries with the highest incidence of type 1 diabetes include Finland and Sardinia [4]. Type 1 diabetes is usually diagnosed in childhood, hence the original classification "juvenile onset diabetes." Indeed, type 1 diabetes accounts for more than 90% of diabetes diagnosed in children and adolescents. Given that the disease is often diagnosed in adults, however, even into advanced age, the term "type 1 diabetes" has been adopted to more accurately reflect the diversity of affected ages. In type 1 diabetes, the primary etiology is due to a cellular-mediated autoimmune-mediated destruction of the β cells of the pancreas. Traditionally, in subjects with type 1 diabetes, autoantibodies may be detected that reflect the underlying attack against these cells [5]. These include autoantibodies to insulin, to GAD65, and to IA-2 and IA-2β (the latter two are tyrosine phosphatases). These antibodies are often detected up to years before the diagnosis of type 1 diabetes [6]. In most subjects with type 1 diabetes, one or more of these antibodies is evident. Indeed, in vulnerable subjects, such as first-degree relatives of affected individuals, the presence of these autoantibodies is often, but not always, a harbinger of the eventual diagnosis of diabetes. Hence, these antibody profiles may be used to predict the risk of diabetes in the siblings and relatives of affected subjects with type 1 diabetes [6].

Genetics of type 1 diabetes

More than forty years ago, type 1 diabetes was found to have very strong links to the human leukocyte antigen (HLA)-encoding genes [7]. The largest study to address this issue was known as the Type 1 Diabetes Genetics Consortium (T1DGC). This group was composed of an international collaboration and amassed more than 14,000 samples [8]. By far, the greatest association to type 1 diabetes was found in the HLA, particularly in the HLA DR-DQ haplotypes. Furthermore, other genes found to have strong genetic association were in polymorphisms identified in the insulin gene [9]. The researchers of T1DGC earlier reported that beyond these two associations, two other loci were found to have odds ratios (ORs) greater than 1.5, and included *PTPN22* and *IL2RA* [9]. However, the ORs for these genes were relatively much lower than that of the HLA region, consistent therefore with the overall strong role of the HLA in the susceptibility to type 1 diabetes.

A number of groups have published the results of genome wide association studies (GWAS) in type 1 diabetes and identified more than 40 potential susceptibility loci in the disease [11]. Candidate genes identified in this approach included those encoding *IL10, IL19, IL20, GLIS3, CD69*, and *IL27*; these are all genes strongly linked to the immune/inflammatory response [10]. In their report, Bergholdt and colleagues integrated the data from these GWAS studies and translated them to a more functional level, that is protein-protein interactions and, finally, they tested their relevance in human islets and in a β cell line, INS-1 cells (rat insulimona-derived cells) [11]. First, they performed a meta-analysis of the type 1 diabetes genome wide Association studies that were available. From these, they identified 44 type 1 diabetes non-major histocompatibility complex (MHC) low density (LD) regions with significance; these regions contained more than 395 candidate genes. They then performed network analysis studies with the intention to more deeply

Table 1.1 Examples of non-HLA type 1 diabetes-associated loci.

Locus	Description	Comments
PTPN22	Protein tyrosine phosphatase, non-receptor type 22	Modulation of T and B cell function
INS	Insulin	Deficient in type 1 diabetes
IL2RA	Interleukin-2 receptor, α	T lymphocyte function
IL10	Interleukin-10	Immunoregulation Inflammation
IL19	Interleukin 19	Immunity/inflammation
GLIS3	Gli-similar 3 protein	Pancreatic β cell generation Insulin gene expression Modulation of pancreatic β cell apoptosis
TRAF3IP2	TRAF3 interacting protein 2	Implicated in IL17 signaling Interacts with members of Rel/NF-κB transcription factor family
PLCG2	Phospholipase C, γ 2	Leukocyte signal transduction NK cell cytotoxicity
CCR5	CC-chemokine receptor 5	Major co-receptor for HIV entry into cells Immune cell recruitment
MYO1B	Myosin 1B	Cell membrane trafficking and dynamics

probe network connections and protein-protein interactions. From this work, 17 protein networks were identified (which contained 235 nodes) containing at least two genes from different type 1 diabetes LD regions [11].

To follow up on these findings, human islets were exposed to pro-inflammatory cytokines and comparisons were made between the treated and untreated human islets (retrieved from eight donors). From this, the following genes were found to be significantly impacted by the cytokine stimulation in the human islets: *IL17RD, CD83, IFNGR1, TRAF3IP2, IL27RA, PLCG2, MYO1B*, and *CXCR7*. Interestingly, the study design suggested that perhaps these traditionally inflammation-associated factors were being produced by pancreatic β cells and not necessarily solely by immune cells. To test this specific point, rat INS-1 cells were treated with cytokines and the above eight genes were examined. Indeed, all but *IL27ra* were identified in the stimulated INS-1 cells [11]. In the case of cultured INS-1 cells, no immune cells are present, therefore suggesting the interesting possibility that these factors may be produced both by islet β cells themselves as well, likely, by infiltrating inflammatory cells. Examples of non-HLA genes linked to type 1 diabetes are illustrated in Table 1.1.

Pathogenesis of type 1 diabetes

There is strong evidence that links the pathogenesis of type 1 diabetes to immune-mediated mechanisms of β cell destruction, including the detection of insulitis, the presence of islet cell autoantibodies, activated β cell-specific T lymphocytes and, as considered above, association of the disease with a restricted set of class II major histocompatibility alleles [12]. Importantly, the rate of the development of type 1 diabetes after the appearance of autoantibodies may be quite variable, reflecting perhaps the contribution of protective mechanisms (such as CD4+–T regulatory cells and other regulatory cells such as invariant

natural killer T [NKT] cells). Such protective factors may differ among individuals, thereby possibly accounting for the variable progression of damaging autoimmunity and the appearance of diabetes. The diagnosis of type 1 diabetes, often made by the appearance of diabetic ketoacidosis [13], is linked to the absence or near absence of plasma C-peptide (N-terminus fragment of insulin that is used to monitor the ability to produce insulin) [14]. It has been suggested that particularly in adults, residual β cell function may be retained for years after the appearance of autoantibodies without manifestation of ketoacidosis. In the sections to follow, we consider some of the specific factors that have been linked to the pathogenesis of type 1 diabetes.

Type 1 diabetes and the environment: infectious agents

As discussed above, the incidence of type 1 diabetes is on the rise at a rate of 3–5% per year that is doubling every 20 years. This is occurring particularly in very young children and is present more often in subjects bearing the low risk alleles [15, 16]. What accounts for these findings? Certainly, genetic risk cannot explain the overall rise in this disorder over relatively short time periods, thereby placing a spotlight on so-called "environmental" factors. For example, it has been suggested that acute infections such as those that are bacterial or viral in nature may precipitate the disease. After such an acute onset, subjects may often enter so-called "honeymoon" periods during which time hyperglycemia abates and the subjects do not require insulin for survival. Examples of viruses linked to type 1 diabetes include cytomegalovirus, coxsackie B, mumps, rubella, Epstein-Barr virus, rotavirus, and varicella zoster virus [17]. An intriguing example of an association between an environmental trigger and type 1 diabetes was speculated to have occurred in Philadelphia in 1993. During the first six months of that year, a substantial rise in the incidence of type 1 diabetes among children was observed. It had been noted that in the two years prior to this event, an outbreak of measles had occurred in the same location, thereby raising the hypothesis that the viral infection stimulated factors that caused type 1 diabetes to emerge in vulnerable children [18].

Type 1 diabetes: the microbiome

In the human intestine, it is estimated that more than 100 trillion bacteria reside and colonize the organ [19]. Far from being a passive factor in the host, these bacteria critically interface with the immune and metabolic systems. Studies have suggested that specific classes of bacteria may exert effects on the immune system. For example, Bacteroidetes were shown to reduce intestinal inflammation [20]. Segmented filamentous bacteria were suggested to induce Th17 immune responses [21]. Th17 immune responses are usually linked to the clearance of extracellular pathogens during periods of infection; Th17 T cells produce major cytokines that induce inflammation such as IL6 and IL8 [22].

In animal models, interference with the normal gut microbiota has impacted the incidence of type 1 diabetes. For example, raising two major mouse and rat models of type 1 diabetes in germ-free or altered flora environments resulted in the animals developing insulitis and type 1 diabetes at accelerated rates [23, 24]. In contrast, feeding type 1 diabetic-vulnerable animals antibiotics significantly delayed or prevented type 1 diabetes [25]. Based on these considerations, the hunt is on to identify

the specific phyla of bacteria that display adaptive/anti-type 1 diabetes impact. So called "probiotics" might one day be identified as treatments to alter the course of type 1 diabetes development, such as the protective effects shown by treatment of type-1-diabetes-vulnerable rats with *Lactobacillus johnsonii* [26].

In the context of the microbiome, it is interesting that type 1 diabetes may appear more frequently in individuals born by Cesarean section vs. natural deliveries [27]. It was shown that in the earliest time of life, the gut microbiome constituents differ in these two states with skin vs. vaginal microbes, respectively, reflecting the major microbiota in subjects born by these two methods. Hence, via Cesarean birth, there is a delay in the colonization of the gut with organisms such as *Bacteroides, Bifidobacterium*, *and Lactobacillus*; the extent to which this might account for increased type 1 diabetes is not clear [28]. The possibility that the distinct phyla of bacteria may influence the types of immune/inflammatory cells in the gut is under consideration as a contributing factor in type 1 diabetes. In this context, type 1 diabetes manifests with an increased number of intestinal inflammatory cells in parallel with reduced numbers of FoxP3 + CD4 + CD25+ T lymphocytes [28]. Hence, it is possible that alteration of the gut microbiota might lead to alterations in immune cell patterns in the gut.

In studies in Finnish subjects with type 1 diabetes, experimental analyses have shown that within the gut microbiome, there is a change in the ratio of two key phyla of bacteria—an increased percentage of Bacteroidetes in parallel with a lower percentage of Firmicutes [29]. Whether this association is linked mechanistically to type 1 diabetes has yet to be clarified. 16S sequencing and metagenomics are current strategies under way to determine if there are actual mechanistic links between alterations in the gut microbiome and the susceptibility to type 1 diabetes.

Type 1 diabetes: vitamin D

Vitamin D, or 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), has been linked at multiple levels to the pathogenesis of type 1 diabetes. Most importantly, vitamin D plays immunomodulatory roles in cells that express the vitamin D receptor (VDR). Included among such cells are antigen presenting cells, activated T cells, and pancreatic islet β cells [30]. Studies have shown that administration of vitamin D or analogues may exert protection against type 1 diabetes in non-obese diabetic (NOD) mice [31]. Experimental studies to discern the underlying mechanisms showed that administration of $1,25(OH)_2D_3$ reduced inflammatory cytokine (such as IL6) production in parallel with increased regulatory T cells. On the contrary, mice deficient in $1,25(OH)_2D_3$ were shown to be at higher risk of developing type 1 diabetes [32].

What is the evidence in human subjects linking vitamin D to type 1 diabetes? Insights into this question became evident in the study of vitamin D receptor (VDR) polymorphisms. The gene encoding the VDR is located on chromosome 12q12-q14 in the human and single nucleotide polymorphisms (SNPs) have been shown to alter the function of the receptor. The results of studies examining these SNPs have yielded contrary data but the largest meta-analysis to date showed that one of the VDR polymorphisms, *BsmI*, was associated with significantly increased risk of T1D but other SNPs, including *FokI, ApaI, and TaqI*, did not display a significant association with T1D [33]. It remains possible that the

VDR locus is not itself the disease affecting locus; rather, the *VDR* may in fact be a marker locus in linkage equilibrium with the true disease locus. Certainly greater functional studies on the SNPs and vitamin D actions are essential to mechanistically link the SNPs to pathological function of the receptor and associations with the pathogenesis of T1D.

What about the levels of vitamin D? Multiple studies in different countries have addressed this question and suggest that lower levels of vitamin D might be related to type 1 diabetes. For example, studies in Switzerland, Qatar, North India, the northeastern United States, and Sweden suggested that levels of vitamin D were lower in type 1 diabetic subjects vs. control subjects. In contrast, in the sun-enriched state of Florida no differences in vitamin D levels were noted between type 1 diabetic subjects and their unaffected first degree relatives and control subjects [30].

Interestingly, support for the North to South incidence of type 1 diabetes emanates from the fact that sun exposure, which is strongly linked to latitude, has possible relationships with type 1 diabetes. Specifically, a number of observational studies have suggested increased type 1 diabetes prevalence in the northern, less sun-exposed latitudes vs. more sun exposed regions. In the EURODIAB study, the incidence of diabetes was found to be higher in the northern region study centers vs. the southern centers, with the exception of Sardinia. Sardinia is considered to be in the southern region but it reported higher rates than those observed in neighboring southern region sites [34, 35]. Not taken into account in these studies are the genetic variations and other vulnerabilities and associations with type 1 diabetes, such as affluence (the latter associated with type 1 diabetes) [36].

The above considerations suggest that supplementation with vitamin D might be protective in type 1 diabetes. When a meta-analysis of multiple observational studies was performed, the results suggested that the incidence of type 1 diabetes was reduced by up to 29% in subjects given supplementation with vitamin D [37]. It is notable, however, that in these studies, concerns regarding many factors, such as reporting of vitamin D levels, doses of vitamin given, and the absence of documentation of vitamin consumption, as examples, limited the overall interpretability of these studies. Hence, a prospective randomized clinical trial is definitely needed to rigorously address these questions and establish possible causality between vitamin D and type 1 diabetes. At this time, no specific answer is available to unequivocally address this issue. Despite these caveats, however, it is essential to address this issue as supplementation with vitamin D should be feasible.

Type 1 diabetes and insulin resistance

In the sections above, we discussed some of the major factors impacting the etiology of type 1 diabetes. Of late, the issue of "double diabetes" has emerged; this term, first employed to describe this concept in 1991, suggests that there is an emergence of insulin resistance in subjects with type 1 diabetes [38, 39]. For example, in type 1 diabetic subjects with obesity or in whom even very high levels of exogenous insulin did not achieve euglycemia, insulin resistance was speculated to be present [38, 39]. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study suggested that a family history of type 2 diabetes significantly predicted excess weight gain in type 1 diabetic subjects [40]. Thus, the degree of peripheral insulin resistance might result from genetic and/or environmental factors (such as energy intake and physical activity).

In fact, in the Pittsburgh cohort of the Epidemiology of Diabetes Complications (EDC) study, there is evidence that the prevalence of obesity has risen significantly in type 1 diabetic subjects, similar to the findings reported in the general population. From 1987 to 2007, this study showed that the prevalence of obesity rose seven-fold and that the prevalence of overweight rose 47% [41]. Although some of these changes might be attributable to insufficient glycemic control in the past decades, the overall premise is that the general increase in obesity/overweight has also impacted the type 1 diabetic subject population.

Finally, it is plausible that the development of insulin resistance might be accounted for, in part, by the route of administration of therapeutic exogenous insulin. When insulin is administered by the subcutaneous route, this has been associated with relative peripheral hyperinsulinemia together with hepatic hypoinsulinemia. Such a regimen might ultimately lead to reductions in peripheral insulin-mediated glucose uptake and increased hepatic glucose production [42]. It remains to be seen which factors may underlie the observed insulin resistance in type 1 diabetes and how these might best be managed in type 1 diabetes.

Type 1 diabetes: summary

In summary, the incidence of type 1 diabetes is on the rise. As Figure 1.1 illustrates, there are multiple contributing factors. Although genetic factors are a major underlying cause, emerging evidence suggests that subjects with traditionally lower genetic risk alleles are being diagnosed with type 1 diabetes. These considerations strongly implicate so-called "environmental" factors in the multiple steps beyond genetic risk that are required before frank type 1 diabetes results. Insights into the interactions between the host and microbiome with respect to modification of genetic risk highlight the complexity of the factors that may significantly modify type 1 diabetes risk.

Type 2 diabetes

Type 2 diabetes is the most prevalent form of diabetes, accounting for up to 90–95% of diagnosed cases of diabetes, and is on the rise [1]. The International Diabetes Foundation (IDF) reported that in the age range of 20–79 years, approximately 285 million adults suffer from diabetes, a number which is expected to rise to approximately 438 million in the year 2030 [2]. In fact, about 90–95% of these cases will be in the type 2 diabetes classification. Older nomenclature referred to this form of diabetes as "non-insulin dependent" or "adult-onset diabetes." In this form of diabetes, at least early in the course of the disease, subjects display insulin resistance with a "relative" deficiency of insulin. However, in the later stages of disease, some subjects are not able to produce sufficient amounts of insulin to compensate for the hyperglycemic stress [1]. This reflects underlying dysfunction of the pancreatic β cell. In type 2 diabetes, ketoacidosis seldom occurs; where it does occur, it may be precipitated by events such as infections. In cases in which very high levels of glucose are present, subjects may present with coma [43].

In general, the risk of developing type 2 diabetes rises with age and is associated with obesity and diminishing physical activity. Type 2 diabetes occurs more frequently in women who displayed gestational diabetes (GDM) during their pregnancies. Further,

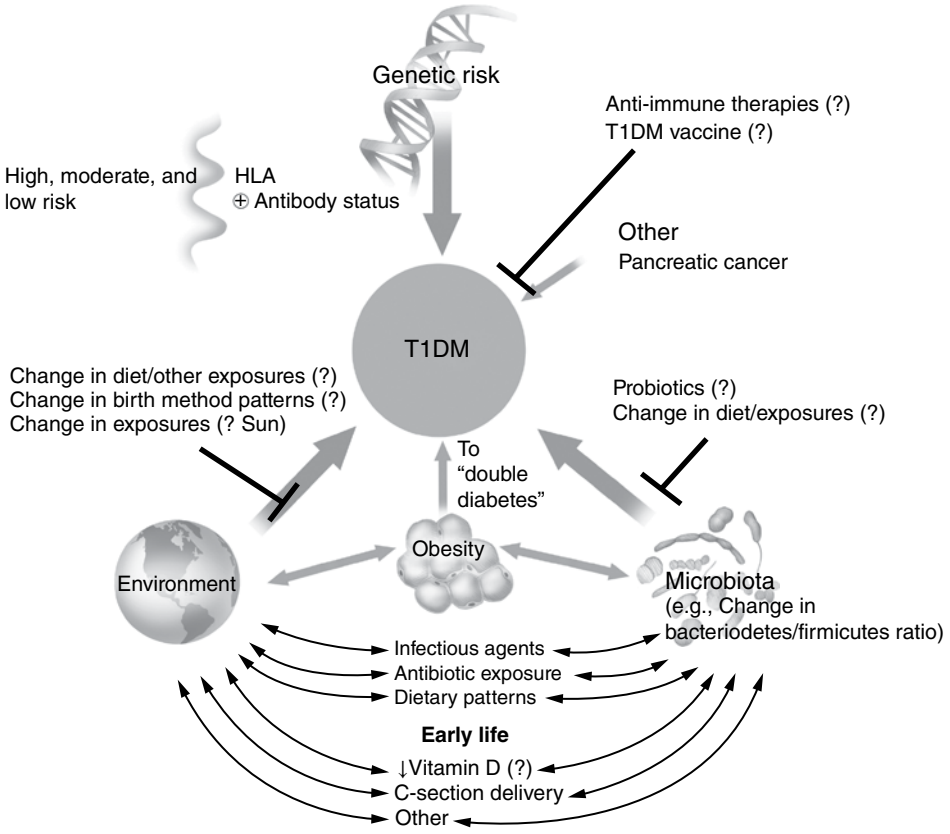

Figure 1.1 Contributory factors to the development of type 1 diabetes. Multiple factors, from genetic risk to environmental influences and perhaps the interface with the gut microbiome, contribute to the pathogenesis of type 1 diabetes. Given that in the vast majority of subjects, genetic risk/antibody status may be discerned and tracked, novel interventions hold promise, ultimately, for the prevention of type 1 diabetes. Dangers in type 1 diabetes, however, include the possible influence of obesity on the rise in "double diabetes." Efforts to minimize possible contributory risks for type 1 diabetes are essential.

epidemiological evidence suggests that the incidence of type 2 diabetes is rising in childhood and adolescence, presumably due to increased obesity and reduced physical activity [44]. In type 2 diabetes, there is a very strong association with genetic factors. Many studies have addressed this issue and will be considered in the sections that follow.

Genetics of type 2 diabetes

The genetics of type 2 diabetes must take into account two key underlying etiologies of the disease, that is, β cell function (insulin secretion) and insulin resistance [1]. In the pre-GWAS era, the strong genetic contribution to type 2 diabetes was determined via family and twin studies [45]. From these efforts, a major gene found to be linked to type 2 diabetes included *CAPN10* (first described in a Mexican-American population) [46].

Others found that regions within chromosomes 5 and 10 were linked to type 2 diabetes, including within the latter, the *TCF7L2* gene [47, 48]. Multiple independent studies confirmed that SNPs in *TCF7L2* were linked to type 2 diabetes. The association of this gene with type 2 diabetes was confirmed in multiple distinct populations [49, 50]. Candidate gene approaches also identified *PPARG* and *KCNJ11* (the latter a potassium inwardly rectifying channel subfamily J member 11) as susceptibility genes for type 2 diabetes [51, 52]. It was not until the GWAS era that more modern and effective approaches were used to identify susceptibility genes in type 2 diabetes.

The first reported GWAS in type 2 diabetes was performed in a French cohort and was composed of 661 cases and 614 control subjects. The number of SNP loci covered in this study was 392,935. From this study, the following genes were identified as association signals in type 2 diabetes: *SLC30A8, HHEX, LOC387761,* and *EXT2*, and the study validated the association of the disease with *TCF7L2* [53]. Following this study, the Icelandic company deCODE Genetics and its colleagues confirmed the association of type 2 diabetes with *SLC30A8* and *HHEX* and added *CDKAL1* [54]. Following this, three collaborating groups (Wellcome Trust Case Control Consortium/United Kingdom type 2 Diabetes Genetic consortium, the Finland-United States Investigation of NIDDM [FUSION] and the Diabetes Genetics Initiative [DGI]) published the findings confirming the association of type 2 diabetes with *SCL30A8* and *HHEX* and added newly discovered associations with *CDKAL1, IGF2BP2*, and *CDKN2A/B* [55–57].

Following these discoveries, the need to increase sample size led to the above groups combining efforts to form the Diabetes Genetics Replication and meta-analysis, or DIAGRAM, consortium. Upon testing of an additional 4,549 cases and 5,579 controls, an additional five loci were discovered including *JAZF1, CDC123/CAMK1D, TSPAN/LGR5, THADA*, and *ADAMSTS9* [58]. By the continued addition of new subjects into these studies, an additional 12 new loci were reported in 2010 [59].

What has emerged from these studies is that many of the type 2 diabetes susceptibility loci are linked to insulin secretion based on human studies examining these loci with functional indices [45]. Hence, it is plausible that pancreatic β cell dysfunction may be a major factor linked to the susceptibility to type 2 diabetes. Examples of genes linked to type 1 diabetes are illustrated in Table 1.2.

The limitations of GWAS have been uncovered by results in a European twin study in which it was found that only approximately 10% of the known type 2 diabetes heritability might be explained by the loci identified in the GWAS [45]. To the extent that SNPs that might be important clues for type 2 diabetes but not be included in the screening modalities will influence missing heritability. In addition, it is quite possible that low-frequency risk variants may indeed possess large effects. Therefore, the next steps include next-generation sequencing strategies such as genome-wide (exome) sequencing [60]. It is hoped that such strategies, as well as utilization of other genetic tools (such as analysis of small RNAs and epigenetics analyses), will fill in the gaps of the missing heritability.

Pathogenesis of type 2 diabetes

In the sections to follow, we will consider the major factors speculated to contribute to the pathogenesis of type 2 diabetes.

Table 1.2 Examples of type 2 diabetes-associated loci.

Locus	Description	Comments
TCF7L2	Transcription factor 7-like 2	Wnt signaling and regulation of glucose metabolism
PPARG	Peroxisome proliferator activated receptor γ	Regulation of lipid and glucose homeostasis, anti-inflammation, and fatty acid oxidation
KCNJ11	Potassium inwardly rectifying Channel J, member 11	Roles in insulin secretion
IGF2BP2	Insulin-like growth factor-2 mRNA binding protein	Binds mRNA encoding IGF2
WFS1	Wolfram syndrome 1	Rare recessive neurodegenerative disorder, one component of which is diabetes
CDKAL1	CDK5 regulatory subunit associated protein1-like 1	Glucose homeostasis; likely roles in insulin secretion and sensitivity
SLC30A8	Soluble carrier family 30 (zinc transporter), member 8	Putative roles in insulin secretion
HHEX	Hematopoietically expressed homeobox	Putative roles in insulin secretion
FTO	Fat mass and obesity associated gene	Roles in methylation, associated with obesity and energy metabolism
HNF1B	Hepatocyte nuclear factor-1beta	Roles in pancreatic exocrine function; related to MODY (maturity onset diabetes of the young)

Type 2 diabetes and obesity

Obesity is considered a major risk factor for the development of type 2 diabetes. How does obesity mediate insulin resistance and diabetes? This is a intensely active area of investigation stimulated by the pioneering studies of Hotamisligil and Spiegelman. They set the stage for linking adipose tissue "inflammation" to insulin resistance in obesity. In 1993, they showed that tumor necrosis factor (TNF)-α mRNA was highly expressed in the adipose tissue of at least four different rodent models of obesity with consequent diabetes and that when TNF-α was neutralized in obese fa/fa rats, insulin sensitivity was improved, as evidenced by increased peripheral uptake of glucose [61]. In 2003, Weisberg and Ferrante showed that obesity in human subjects and in animal models was associated with increased infiltration and/or retention of macrophages in the perigonadal, perirenal, mesenteric, and subcutaneous adipose tissue [62]. Ferrante's later work linked CCR2 and its chemoattractant functions to the increased infiltration of macrophages to adipose tissue in high fat feeding in mice [63]. Further work on the macrophage populations by Olefsky and colleagues suggested that expression of CD11c was a key contributor to obesity-associated insulin resistance [64]. Other studies have suggested that macrophage populations cause increased activation of NF-κB and JNK MAP kinase signaling pathways, both linked to insulin resistance [65, 66]. Various genetic modification studies in mice suggest