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Diabetes and oral disease: implications for health professionals

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Abstract

"Diabetes and Oral Disease: Implications for Health Professionals" was a one-day conference convened by the Columbia University College of Dental Medicine, the Columbia University College of Physicians and Surgeons, and the New York Academy of Sciences on May 4, 2011in New York City. The program included an examination of the bidirectional relationship between oral disease and diabetes and the inter-professional working relationships for the care of people who have diabetes. The overall goal of the conference was to promote discussion among the healthcare professions who treat people with diabetes, encourage improved communication and collaboration among them and ultimately, improve patient management of the oral and overall effects of diabetes. Attracting over 150 members of the medical and dental professions from eight different countries, the conference included speakers from academia and government and was divided into four sessions. This report summarizes the scientific presentations of the event.

Keywords

diabetes; oral disease; meeting report

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Conflicts of interest
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Introduction

A large portion of the U.S. population has periodontal disease and this prevalence is significantly increased in individuals with diabetes. Evidence also suggests that diabetes leads to worsening periodontal disease and in turn, the systemic inflammation and infection that may result from periodontal disease can have an adverse effect on glycemic control and health outcomes, thus creating a cycle that compromises diabetes management in affected individuals. Any improvement in glycemic control and/or periodontal disease has the potential to make a significant impact on the quality of life for individuals with diabetes. Comprehensive diabetes care is a team effort involving both the patient and a system of health care professionals. Improved communication between medical and dental care professionals can improve patient management of the oral and overall effects of the disease.

Recently a symposium was held at The New York Academy of Sciences entitled “Diabetes and Oral Disease: Implications for Health Professionals” during which the bidirectional relationship between oral disease and diabetes was examined. The symposium’s objective was to provide an opportunity for interactive and interdisciplinary discussion and education that would lead to enhanced quality of health-care delivery, improved patient outcomes, and also serve as an impetus for medical and dental care professionals to coordinate and collaborate towards the goal of improving the health of individuals with diabetes.

Current concepts in diabetes

William C. Knowler, MD, DrPH, (National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health) opened the symposium with a presentation entitled the “Diabetes Epidemic and the Need for Collaborative Healthcare Delivery”.

To begin, Knowler spoke about the seriousness of diabetes as a chronic disease and explained that diabetes prevalence is dramatically increasing in most parts of the world. Morbidity and mortality, due to each major type of diabetes (type 1 and type 2), he continued, are primarily due to the long-term complications that have long been recognized to affect the eyes, kidneys, heart, blood vessels, and nerves. In addition, Knowler explained, while long recognized as a complication of type 1 diabetes, periodontitis is also a complication of type 2 diabetes.[1,2] Periodontitis, he continued, is important not only for oral health, but also for its association with many adverse health outcomes, presumably because it is accompanied by systemic inflammation. This seems to be supported, Knowler explained, by the findings from a longitudinal population study of Pima Indians ≥ 35 years old in which diabetes and periodontal disease were assessed objectively. The researchers involved in this study reported that age-and sex-adjusted death rates from natural causes among diabetic persons were 3.7 deaths per 1000 person-years (95% confidence interval 0.7 to 6.6) in those with no or mild periodontal disease, 19.6 (10.7 to 28.5) in those with moderate periodontal disease, and 28.4 (22.3 to 34.6) in those with severe periodontal disease[3](Fig. 1). This relationship remained significant when adjusted for numerous potentially confounding factors.

Knowler continued by turning his attention to the prevention of diabetes. He explained that the adverse consequences of periodontal disease in diabetes, as with all diabetes complications, would presumably be minimized or prevented if diabetes itself could be prevented. The prospects of preventing diabetes, Knowler continued, vary with the type of diabetes. The American Diabetes Association, he explained, classifies diabetes into two major types: 1 and 2 (Ref. 4). Type 1 diabetes is due to autoimmune or idiopathic destruction of the pancreatic beta cells. Type 2 diabetes results from a combination of defects in insulin secretion and insulin action. Research in prevention of type 1 diabetes, Knowler explained, has focused on immune modulation, but so far has not met with

reproducible success. By contrast, he continued, prevention research in type 2 diabetes, including lifestyle modification aimed at weight loss and increased physical activity or drugs affecting insulin resistance or secretion, has been at least partially successful.[5-7] Because of the complex set of causes of diabetes, research in diabetes prevention, Knowler concluded, requires a multidisciplinary scientific approach, and because diabetes affects many organ systems, preventing and treating diabetes complications requires collaboration among many health care professionals, including those in oral health.

Rudolph L. Leibel, MD, (Naomi Berrie Diabetes Center, Columbia University College of Physicians and Surgeons) divided his presentation into two parts. First, he focused on type 2 diabetes. Leibel explained that the prevalence of type 2 diabetes is increasing rapidly in virtually all parts of the world and interestingly, this increase almost perfectly parallels an increasing prevalence of obesity. Neither of these relatively acute processes can be the result of recent genetic changes, Leibel explained, but rather, both reflect the consequences of genetic selection exercised on human populations. As a species designed for environments in which high levels of physical activity and efficient storage of calories were required and in which lifespan was quite short, Leibel explained, we have clearly succeeded in creating man-made environments in which all of these predicates are eliminated. The consequences, he continued, are pandemic obesity and type 2 diabetes.

The genes predisposing to fat accumulation and beta cell dysfunction appear to be largely distinct[8,9] Leibel explained. As a general formulation, Leibel continued, the pathogenesis of type 2 diabetes involves interactions of multigenic susceptibilities of beta cells to metabolic stress with environmental factors that cause that stress. Obesity, by increasing resistance to insulin action and hence the need for insulin production by a limited number of beta cells, is perhaps the most important single stressor at present, Leibel explained. The prevention of type 2 diabetes in individuals with impaired glucose tolerance, by exercise and weight reduction (NIH Diabetes Prevention Program, DPP, Study),[10] and the reversal of recent onset type 2 diabetes in obese individuals by moderate degrees of weight loss,[11] clearly demonstrates, Leibel explained, the functional relationship between obesity and type 2 diabetes. Other environmental factors, he pointed out, include intrauterine exposure to hyperglycemia and obesity, diet composition, and levels of fitness.

One of the major problems in applying a logical inference of these insights, Leibel continued, is that maintenance of a reduced body weight is extremely difficult for most patients. Part of the reason for this difficulty, he continued, is the body's homeostatic mechanisms for the defense of body fat. These defenses are part of the evolutionary biology and involve responses to reduced body weight that include reduced energy expenditure and increased drive to eat[12] Leibel explained. Full understanding of the physiology of these responses should lead to more effective prevention and treatment of obesity, and hence of type 2 diabetes, concluded Leibel.

In the second part of his presentation, Leibel spoke about type 1 diabetes. Leibel first stated that type 1 diabetes is an autoimmune form of diabetes, with worldwide prevalence about 10% that of type 2 diabetes. And, like type 2 diabetes, the prevalence of this type of diabetes is also increasing, though not as rapidly. Like type 2 diabetes, Leibel explained, gene-by-environment interactions are dispositive. Most of the genetic susceptibility (and resistance), he continued, is conveyed by HLA genotypes that, in turn, mediate cellular immune responses to antigens that include insulin, but also environmental antigens not yet fully understood.[5,13] The natural history of type 1 diabetes, Leibel explained, includes a generally prolonged "run in" to the disease, as beta cell mass is inexorably reduced by cellular immune assault on the beta cells of the islets of Langerhans. There is evidence, he continued, that even in individuals with longstanding, insulin-requiring type 1 diabetes,

residual beta cells are present in islets, resulting from ongoing beta cell divisions that are simply not able to keep up with the persistent immune assault. The ability to enhance beta cell replication to the point where the destructive process is outstripped could, Leibel continued, constitute an effective intervention. Likewise, suppression of the immune assault to the point where replication could compensate, would be an alternative or synergistic approach. Finally, Leibel stated, the advent of techniques to generate stem cells and to drive them towards beta cell phenotypes could ultimately provide a source of beta cells that might be used to replace those subjected to immune destruction. These cells, if derived from a patient with type 1 diabetes, he explained, would likely still display the immune epitopes that are driving continued destruction of native beta cells. Steps would be required to silence the expression of these epitopes, or the presence of immunocytes directed at them, or both.

Our increasing understanding of the genetic underpinnings of these two forms of diabetes, Leibel stated, enable us to “fix” these contributors in ways that enable clearer understanding of the environmental factors (and their mechanisms of action) that mediate the timing and severity of expression (“penetrance”) of these genetic predispositions. Likewise, better understanding of the specifics of the environmental contributions permits better understanding of the mechanisms of genetic susceptibility. Science that exploits these reciprocal relationships, Leibel concluded, is the most likely to lead us to the insights required to prevent and cure these diseases.

The diabetes–oral disease connection

George W. Taylor, DMD, DrPH, (University of California at San Francisco School of Dentistry) presented on the bidirectional relationship between diabetes and periodontal disease. Taylor provided an epidemiologic perspective by reviewing the evidence for the adverse effects of diabetes on periodontal health, the role of periodontal infection in adversely affecting glycemic control, the impact of periodontal therapy on improving glycemic control, and the relationship of periodontal infection to the risk for developing diabetes complications, and possibly diabetes itself.

Taylor focused on some of the longitudinal observational studies that have provided evidence to support both the adverse effects of diabetes on periodontal health and those of severe periodontitis on increased risk for poorer glycemic control and diabetes complications.[14] He explained that the studies of the effects of non-surgical periodontal therapy on glycemic control are a heterogeneous set of reports that include randomized clinical trials (RCTs) and clinical intervention studies that are not RCTs. Of the RCTs reported in the literature, Taylor indicated that several reported a beneficial effect for periodontal therapy although some RCTs did not. Recent meta-analyses of the intervention studies, Taylor explained, provided supporting evidence that non-surgical periodontal therapy improves glycemic control, particularly in type 2 diabetes, with an average reduction of hemoglobin A1c of approximately 0.4% in pooled analyses[15,16](Table 1). Taylor pointed out, is a clinically important improvement because for each 1% reduction in mean HbA1c level, a 14% to 21% reduction in diabetes-related end points has been reported.[17]

In addition, Taylor spoke about the emerging evidence, from a small number of longitudinal observational studies, that suggests that periodontal disease is associated with increased risk for diabetes complications, including cardiovascular disease,[18] cardio-renal mortality,[3] and renal disease.[19] Taylor reported, that there is evidence that periodontal infection may be a risk factor for the development of diabetes.[20]

Taylor provided a brief description of each study and their findings. One study, conducted by Saremi and colleagues,[3] followed a cohort of 628 Pima Indians in Arizona, USA, for a

median follow-up time of 11 years. The researchers found those with severe periodontal disease at baseline had 3.2 times greater risk for cardio-renal mortality than those with no, mild, or moderate periodontal disease. This estimate of significantly greater risk included controlling for several recognized major risk factors of cardio-renal mortality. A second study, Taylor explained, investigated the effect of periodontitis on risk for development of overt nephropathy (macroalbuminuria) and end-stage renal disease (ESRD) in a group of 529 Gila River Indian Community adults with type 2 diabetes. Shultis and colleagues,[19] found the incidence of macroalbuminura was 2.0, 2.1, and 2.6 times greater in individuals with moderate or severe periodontitis or in those who were edentulous, respectively, than those with none/mild periodontitis. The incidence of ESRD was also 2.3, 3.5, and 4.9 times greater for individuals with moderate or severe periodontitis or for those who were edentulous at baseline, respectively, than those with none/mild periodontitis.

Demmer and colleagues,[20] according to Taylor, investigated the association of periodontal disease with the incidence of type 2 diabetes in over 7,000 participants of the First National Health and Nutrition Examination Survey (NHANES I) and the NHANES Epidemiologic Follow-up Survey. They reported a positive association between baseline periodontal disease and incident type 2 diabetes in a cohort study of individuals who were followed for a mean of 17 years. In addition, they found that periodontal disease was significantly associated with 50–100% greater risk for type 2 diabetes incidence at follow-up, after adjusting for other recognized risk factors for the development of type 2 diabetes.

In his conclusion, Taylor pointed out that the evidence, to date, supports the bidirectional, adverse relationship between periodontal infection and diabetes and that given the current evidence, it would be prudent to consider treating periodontal infection in people with diabetes as an important component of their overall management plan for diabetes care. However, Taylor emphasized that further rigorously conducted randomized clinical trials are necessary to unequivocally establish that treating periodontal infections can contribute to glycemic control and to the reduction of the burden of diabetes complications.

Ira B. Lamster, DDS, MMSc, (Columbia University College of Dental Medicine) also briefly spoke about the association between periodontal disease and diabetes, but his presentation focused on the other oral and craniofacial disorders that have been identified as associated with diabetes. Lamster explained that in addition to periodontal disease, dental caries, burning mouth syndrome, Candida infection, salivary dysfunction/xerostomia, taste and other neurosensory disorders, altered tooth eruption and benign parotid hypertrophy all have been reported to be associated with diabetes.

The relationship of diabetes and oral health has an extensive literature that has been widely disseminated. Much of it, explained Lamster, has focused on periodontal disease, and comprehensive reviews have demonstrated increased severity of periodontal disease is associated with diabetes mellitus.[14] Further, according to Lamster, there is reasonable evidence to suggest that periodontitis is associated with poor metabolic control of diabetes, and that in the absence of other treatment, periodontal therapy can lead to a significant improvement in metabolic control (i.e. reduction in HbA1c) for a limited period of time (3 months).

Less attention, however, according to Lamster, has been focused on the other oral complications of diabetes, yet it is essential that dental practitioners be aware of these disorders. Further, most of the clinical research, Lamster explained, has focused on young to middle-aged adults (25 to 55 years of age), with relatively limited research on younger individuals, or older adults.

Research from Columbia University, Lamster reported, has shown that children and adolescents with diabetes (age range of 6 to 18 years), demonstrate evidence of periodontal destruction. When compared to controls without diabetes the relative risk of periodontal destruction was 2.72 (entire cohort, $P = 0.006$). When analyzed by age, younger individuals (ages 6–11) demonstrated greater risk (3.74, $P = 0.21$) then older individuals (ages 12–18; 2.63, $P = 0.066$).[21] Examining the relationship of diabetes-related parameters to the risk for periodontal destruction in this cohort of young patients with diabetes revealed that HbA1c was significantly associated with periodontitis, whereas duration of diabetes and BMI for age percentile were not.[22] Another report in this series of studies, Lamster explained, indicated that tooth eruption occurred sooner in young patients with diabetes as compared to non-diabetic controls. This occurred later in the eruption sequence (the extra-alveolar phase of tooth eruption).

With the aging of the population, the increased prevalence of diabetes in older adults, and the increased prevalence of oral diseases in the elderly, studying oral manifestations of diabetes mellitus in older adults is both important and subject to confounding said Lamster. Some of the more recent findings he reported included the following:

1. Coronal caries were comparable in cases and controls, but the prevalence of root caries was higher in patients with diabetes. Similarly, salivary flow was comparable in cases and controls, but the effects of xerogenic medications was more pronounced in patients with diabetes than controls.[23]
2. For older edentulous patients with diabetes, a greater prevalence of burning mouth syndrome, dry mouth, angular cheilitis and glossitis was observed as compared to controls.[24]
3. Benign parotid hypertrophy has been reported in older patients with diabetes. The prevalence is unknown, but preliminary evidence suggests that this is related to an enlargement of acinar cells, perhaps associated with an interruption in protein synthesis and release.

Lamster concluded his presentation by pointing out that a great deal has been learned about the oral complications of diabetes, but that much remains to be studied. The variety of oral lesions associated with diabetes, Lamster explained, emphasizes the importance of these disorders for patients, and for the dental professionals who care for them.

Karen Novak, D.D.S., M.S., Ph.D. (American Dental Education Association) presented ongestational diabetes mellitus and periodontitis and examined the possible link between these two conditions and maternal/fetal negative outcomes. Novak began by explaining that gestational diabetes mellitus (GDM) is a type of diabetes that develops during pregnancy and may or may not continue following parturition. Of the diabetes seen in pregnancy, only 10% is pre-gestational with the remaining 90% being gestational.[25] GDM affects approximately 135,000 pregnant women (3–5%) annually in the United States, Novak explained, making it the most common metabolic disorder and medical complication of pregnancy.[26] Defined risk factors for development of GDM, she continued, include obesity, a family history of diabetes, having given birth previously to a very large infant, a still birth or a child with a birth defect, having too much amniotic fluid (polyhydramnios) and being older than 25 years of age.[27]

Women with GDM make sufficient amounts of insulin Novak explained, however, placental hormones (e.g. estrogen, cortisol, human placental lactogen), block the effect of insulin leading to “insulin resistance.” This begins, Novak continued, about midway (20–24 weeks) through pregnancy. The larger the placenta grows, the more these hormones are produced, and the greater the insulin resistance becomes. In most women the pancreas is able to make

additional insulin to overcome the insulin resistance, but when the pancreas makes all the insulin it can and there still is not enough to overcome the effect of the placenta's hormones that is when GDM results Novak explained.[28,29]

GDM, Novak continued, can have a negative impact on both the mother and the fetus. Negative maternal outcomes associated with gestational diabetes include pre-eclampsia (hypertension), premature rupture of membranes, Caesarean section, and pre-term delivery.[30-32] Although GDM develops or is discovered during pregnancy, and usually disappears when the pregnancy is over, 30–50% of women who have had GDM, Novak explained, develop documented type 2 diabetes 3–5 years post-partum.[33,34] Moreover, greater acute and chronic neonatal morbidity and mortality have been described in neonates delivered by women with GDM.

There is substantial evidence available documenting that the severity of periodontal disease is increased in patients with type 2 diabetes,[14,35] Novak pointed out, but minimal data are available on the effects of GDM on periodontal health. In addition, although substantial data have been accrued to support earlier observations that the infection and inflammation associated with periodontal disease may have a negative impact on the period of gestation and on fetal growth[36-38] there are limited data, Novak continued, on the relationship between diabetes, periodontal disease and pregnancy outcomes (combined effect). It was with this in mind, Novak explained, that she and her colleagues set out to study the hypothesis that women with GDM are at higher risk for developing more severe periodontal disease than women without GDM and that the combination of GDM and periodontal disease will be associated with an increased negative impact on maternal and fetal health.

Novak continued her presentation by describing the study in which she was involved. She explained that women with GDM and non-GDM pregnant controls were recruited from the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology at the University of Kentucky. Subjects were matched based on age, gestational age and race/ethnicity. Comprehensive medical and dental histories were obtained and a periodontal examination, consisting of plaque index, probing pocket depths (PD), clinical attachment levels (LOA), bleeding index (BOP) and calculus index, was completed. Patients were further categorized as either having or not having periodontal disease. Periodontal disease was defined, Novak explained, as having at least 4 teeth with PD ≥ 4 mm, LOA ≥ 2 mm and BOP. Post-delivery maternal outcomes were evaluated as a composite, with the presence of any one of the following being a recorded negative outcome: pre-eclampsia, premature labor, premature rupture of membranes, urinary tract infections, chorioamnionitis/funisitis, induction of labor, operative vaginal deliveries or unplanned cesarean.[39] Similarly, fetal outcomes, Novak continued, were evaluated as a composite, with the presence of any one of the following constituting a negative outcome: intrauterine growth restriction/low-birth-weight, shoulder dystocia, brachial plexus damage, facial nerve injury, fractured bones, other neonatal birth problems, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, transient tachypnea of the newborn, polycythemia, hypocalcemia, intraventricular hemorrhage, necrotizing enterocolitis, congenital anomaly, stay in NICU, Apgarat 1 minute or Apgar at 5 minutes of less than 7. Multiple logistic regression analyses, adjusted for smoking and calculus as known risk factors associated with periodontal disease, Novak explained, will be used to calculate odds ratios for adverse maternal and fetal outcomes. Women with periodontal disease and gestational diabetes will serve as the reference group.

Thomas W. Oates, DMD, PhD, (University of Texas Health Science Center at San Antonio), presented on diabetes and its impact on dental implant therapy. Oates explained that periodontal disease frequently results in tooth loss, with the cumulative effects most significant in older patients. It is these older patients, Oates explained, who are also

particularly susceptible to type 2 diabetes and its comorbidities, that diabetes has been shown to significantly increase the levels of periodontal disease and tooth loss. Thus, Oates explained, one of the more subtle complications of diabetes may be a decrease in a patient's quality of life due to tooth loss and compromised masticatory function.[40]

Oates pointed out that oral health is an integral part of nutritional well-being and systemic health. Chronic diseases such as diabetes, he explained, have oral sequelae that may lead to compromises in oral function, and oral function may importantly modulate dietary interventions critical to the overall management of diabetes.[23] From a medical standpoint, there is no doubt that long-term good glycemic control is critical to the patient's minimizing diabetes related co-morbidities. However, good glycemic control may be dependent upon proper masticatory function Oates explained. With diabetes contributing to oral pathologies and tooth loss, tooth replacement as can be provided with implant therapy may be an important contributor to the patient's overall well-being Oates pointed out. While diabetes remains a relative contraindication to implant therapy based on glycemic control, there are no strong clinical data supporting increased implant failures for patients lacking good glycemic control. In fact, Oates reported, more recent studies support the use of dental implant therapy for diabetic patients even in the absence of good glycemic control.[41-44] Therefore, Oates explained, with the potential benefit implant therapy has to offer, it may be in the diabetes patient's best interest to consider implant therapy. While this represents a shift in attitudes toward diabetic patient care, it is one that requires careful consideration of the risks and benefits of care, as well as the limitations in our understanding of this relationship Oates concluded.

Unraveling the mechanistic links between periodontitis and diabetes

Ann Marie Schmidt, MD, (New York University School of Medicine) presented on the role played by the receptor for advanced glycation endproducts (RAGE) and inflammation in diabetic complications including periodontal disease.

Schmidt began her presentation by first providing some information about RAGE. RAGE she explained is a multi-ligand receptor of the immunoglobulin superfamily. It was discovered as a receptor for advanced glycation endproducts (AGEs), the products of nonenzymatic glycation and oxidation of proteins and lipids that accumulate in diabetes. RAGE, Schmidt explained, also binds proinflammatory ligands, such as members of the S100/calgranulin family, high mobility group box 1 (HMGB1) and amyloid-β peptide and β-sheet fibrils.[45] Strategies to block RAGE, such as soluble RAGE, the extracellular ligand-binding decoy of the receptor, or genetically-modified mice, such as homozygous RAGE null animals, Schmidt continued, have been employed in various animal models of diabetes and its complications. These studies revealed that RAGE plays key roles in the development of macro- and microvascular complications in diabetes.[45] In this context, subjects with diabetes Schmidt explained, display increased severity of periodontal disease.

Schmidt continued her presentation by reporting on the findings of her and her colleagues. She explained that she and her fellow researchers were able to show that RAGE and AGEs were expressed in human diabetic gingival tissue retrieved at the time of periodontal surgery, and co-localized to both vascular and inflammatory cells.[46] Schmidt went on to explain that, as similar findings were observed in diabetic mice inoculated by oral/anal gavage with the periodontal pathogen *Porphyromonas gingivalis (Pg* 381), she and her colleagues tested the role of RAGE in periodontal disease in diabetic mice. They observed, Schmidt reported, that compared to non-diabetic mice, diabetic mice displayed significantly greater degrees of alveolar bone loss and gingival inflammation; in parallel, levels of gingival tissue inflammation and matrix metalloproteinases were higher in the diabetic

tissues. Consistent with contributory roles for RAGE, administration of soluble RAGE suppressed exaggerated gingival inflammation, matrix metalloproteinase activity and alveolar bone loss *Pg* 381–infected mice.[47]

Schmidt concluded her presentation by reporting on a recent study by Lalla and colleagues. In this study, Schmidt explained, the researchers addressed whether RAGE contributed directly to vascular inflammatory stress stimulated by *Pg* 381. During the study, endothelial cells were retrieved from the aortas of wild-type or RAGE null mice and infected with *Pg* 381.When wild type endothelial cells were treated with *Pg* 381, increased expression of RAGE, levels of AGEs and monocyte chemoattractant peptide-1 (MCP-1) resulted; however, in RAGE null endothelial cells *Pg* 381 did not elicit these findings.[48] Upregulation of these inflammatory mediators, Schmidt reported, was also prevented by infection with DPG3, a fimbriae deficient mutant of *Pg* 381, thereby suggesting, Schmidt explained, that RAGE might contribute to invasion of this microorganism. Further experimentation, Schmidt conceded, is required to address this point.

Taken together these data, Schmidt explained, link RAGE to *Pg*-dependent mechanisms that both destroy alveolar bone and stimulate endothelial cell stress—processes linking RAGE to the causes and consequences of periodontal inflammation and damage.

Dana T. Graves, DDS, MSc, (University of Pennsylvania School of Dental Medicine) spoke about the impact of diabetes on inflammation, cell death, and bone in periodontal disease. Graves explained that diabetes mellitus is a metabolic disorder associated with several complications including impaired healing. An important aspect of diabetes, and related to impaired healing, he explained, is the increase in production of pro-inflammatory mediators, which include, reactive oxygen species (ROS), advanced glycation endproducts and cytokines such as TNF-α. Graves continued by explaining that the penetration of bacteria into connective tissue produces a significantly elevated inflammatory response in diabetic animals compared to non-diabetic controls. Microarray analysis further indicates that bacteria stimulate greater up-regulation of a number of pro-inflammatory and pro-apoptotic genes in diabetic animals compared to normoglycemic controls. This, Graves explained, is due to a general dysregulation of cytokines upon bacterial perturbation, which can be reversed by inhibition of TNF;[49] a factor that has significant implications in both wound healing and periodontal disease. Soft tissue wounds of the skin and gingiva in diabetic animals are characterized by greater levels of inflammation, reduced proliferation and greater apoptosis.[50] These aspects of diabetic wound healing can be reversed by inhibition of TNF-α, mechanistically linking reduced proliferation, greater apoptosis and impaired healing to the effect of enhanced inflammation that is found in diabetic wounds.

Graves continued his presentation with an overview and examination of the impact diabetes has on periodontal disease. He explained that periodontal disease is significantly greater in individuals with diabetes and that it has been reported that diabetes increases the risk as well as the severity of periodontal disease. This position, Graves pointed out, is also evident in several animal models of diabetes. Diabetic animals, Graves explained, exhibit enhanced bone loss and greater inflammation in experimental periodontitis.[47,51] In particular, diabetes appears to cause prolonged inflammation in various animal models following exposure to periodontal pathogens suggesting difficulty in down regulating the inflammatory response. Graves reported that he and his colleagues investigated whether diabetes primarily affects periodontitis by enhancing bone loss or by limiting osseous repair using a ligature induced model in the type 2 Zucker diabetic fatty (ZDF) rat and normoglycemic littermates.[51] They found that diabetes increased the intensity and duration of the inflammatory infiltrate. In addition, they found that while the formation of osteoclasts and bone resorption was initially similar in the diabetic animals, after the etiologic factor was removed, osteoclastogenesis

persisted in the diabetic animals while it quickly returned to normal levels in the normoglycemic group. Moreover, Graves explained, the impact of diabetes on bone loss in periodontitis is further enhanced by interfering with coupled bone formation. Following an episode of periodontal bone loss a certain amount of resorbed bone is regained by coupled bone formation. Bone coupling occurs, he explained, because bone is programmed to undergo a process of repair following bone loss leading to a discrete level of regeneration. In experimental periodontitis, however, the amount of bone formation that occurs is incomplete and does not equal the amount of bone resorbed leading to net bone loss.[49] When the amount of new bone formation following resorption was measured in diabetic and normoglycemic animals, Graves explained, the level was found to be 2.5-fold higher in the normal group ($P < 0.05$). Diabetes also increased apoptosis in bone-lining cells and periodontal ligament fibroblasts ($P < 0.05$). Thus, Graves explained, diabetes caused a more persistent inflammatory response, greater loss of attachment, more alveolar bone resorption, impaired coupled bone formation and increased net bone loss. Graves concluded by reporting that recent studies indicate that diabetes can affect coupled bone formation by reducing proliferation in bone lining cells and by reducing the expression of growth factors that stimulate these cells including basic fibroblast growth factor and transforming growth factor-beta.

Figure 2 presents a model of the potential mechanisms discussed by Schmidt and Graves in this session.

Inter-professional relationships in patient care

Evanthia Lalla, DDS, MS, (Columbia University College of Dental Medicine) began her presentation by stating that in order to provide comprehensive care to people who have diabetes, there must be a team effort that involves the patient and various healthcare professionals. This group effort in the management of affected individuals is essential, if more efficient and effective care is to be achieved.

The effort essentially begins with the patient, Lalla explained. The patient with diabetes needs to commit to self-care, make ongoing decisions regarding self-care and communicate frequently and honestly with healthcare providers. The healthcare professionals' role in the team effort, Lalla continued, is to provide their diabetic patients with guidance in goal setting, suggest strategies and techniques on how to achieve goals and overcome barriers, provide skills training (self-management techniques), screen, and manage the risk, for complications.

Dental professionals in particular, Lalla continued, must discuss with their patients about the link between oral and general health, how diabetes and periodontitis interrelate, and about the need for co-management of their condition by multiple healthcare providers, as studies suggest that oral disease awareness among diabetic individuals is rather low.[52-57] They must also promote lifestyle changes and good oral and overall health behaviors. Special considerations in the treatment of dental patients with diabetes must also be taken into account, in order to ensure that the oral care provided is safe and that therapeutic outcomes are predictable. These considerations include taking a thorough medical history, establishing communication with the treating physician, and performing a careful intraoral evaluation, including a comprehensive periodontal assessment. Initial therapy, Lalla continued, should focus on the control of acute infections and a less complex, stepwise therapy plan should be offered when possible. Prevention, early recognition and proper management of emergencies also are very important for dental professionals to address Lalla pointed out. Dentists, she explained, need to remember that for all people with type 1 and many with advanced type 2 diabetes hypoglycemia is a fact of life. Hyperglycemic crisis is less

common, but serious. Dental professionals therefore, Lalla explained, must consider timing and duration of appointments, possible need for change in diabetic regimen in consultation with the treating physician, and provide profound anesthesia and pain control in conjunction with procedures and along with any antibiotic or host modulation agents. Clinical protocols and guidelines should be in place in every dental practice setting for determining frequency of follow-up care, determining the need for referral to a dental specialist and the need for medical consultation, referral and follow-up.

Lalla continued her presentation by turning her attention to the growing number of people in the United States who have diabetes, but who remain undiagnosed. She explained that 70% of Americans see a dentist at least once per year[58] and that these patients often return for multiple, non-emergency, visits. This, according to Lalla, suggests that dental settings can also be healthcare locations actively involved in screening for unidentified diabetes. Dental professionals, Lalla explained, can assess risk factors, refer for testing or "formally" screen, and follow-up on outcomes. Borrell and colleagues,[59] Lalla continued, first explored the ability of clinical periodontal findings coupled with self-reported information readily obtained during an individual's medical history review to identify patients with undiagnosed diabetes (i.e. those with an FPG ≥ 126 mg/dl among those who responded negatively to the question "Have you ever been told by a doctor that you have diabetes?"). Data from NHANES III public-use files (4,830 subjects ≥ 20 years of age) were used to calculate the predicted probability of having undiagnosed diabetes and findings suggested that such an approach is promising. This was subsequently corroborated by two other NHANES-based studies.[60,61] The first study, Lalla reported, to prospectively collect data in a clinical setting in order to single out a simple and efficient protocol to identify people with undiagnosed pre-diabetes or diabetes revealed that two dental parameters (number of missing teeth and percent of deep periodontal pockets) were effective in correctly identifying the majority of cases of unrecognized dysglycemia.[62] The addition of a point of care HbA1c test result, Lalla continued, was found to significantly improve the performance of the screening algorithm in the population under investigation.

As to the role of medical care providers, Lalla reported that the evidence to date suggests that physicians and nurses do not receive adequate training in oral health, are not comfortable performing a simple periodontal examination and rarely advise patients on aspects of oral health.[63-67] Medical care providers, Lalla stated, need to discuss with their diabetic patients the importance of oral health and its relationship to diabetes and the potential sequelae of long-standing, untreated oral infections. All diabetic patients, she continued, should be advised to see a dentist on a regular basis. Screening for oral/periodontal changes must be part of the assessment of diabetic patients, similarly to the screening for other complications. Asking about symptoms and performing a visual assessment of the mouth is simple, Lalla explained and should be a part of the medical provider – patient interaction. In addition, medical care providers should also facilitate communication with the treating dentist by offering information on patients' medical background, level of glycemic control, presence of other complications and co-morbidities; and they should be available to offer advice on medical management modifications that may be necessary.

An inter-disciplinary approach and collaboration beyond professional boundaries, Lalla concluded, must become the standard of care for the management of the patients with or at-risk for diabetes.

Carol Kunzel, PhD, MA (Columbia University College of Dental Medicine) presented on her work, which examined "Dentists' Attitudes and Orientations in the Management of the Patient with Diabetes". Kunzel began her presentation by explaining that because diabetes is

a risk factor for periodontal disease, dentists can help reduce this risk by assessing, advising, and closely monitoring the diabetic patient. In doing so, Kunzel explained, dentists assume functions characteristic of primary and preventive health care clinicians. Thereby, the dental setting, Kunzel proposed, can be a health care location actively involved in identifying undiagnosed diabetic patients and assisting in the better management of diagnosed patients with diabetes.

In previous work, Kunzel explained, she and her colleagues thought of this active dentists' involvement as having three phases: assessment, discussion, and active management.[68] Assessment, she explained, constitutes dentists asking the diabetic patient about the type and severity of disease; discussion represents their communication with the patient; and active management reflects actions taken to ameliorate the diabetic patient's oral health care. Kunzel explained that she and her colleagues investigated dentists' performance of these activities, and their attitudes toward performing them, via a mail survey of representative samples of randomly selected dental general practitioners and periodontists in the northeast US (GP response rate = 80%; Periodontist response rate = 73%). Sample members were mailed a 4-page questionnaire containing closed-ended items concerning attitudes and orientations regarding performing the three types of involvement, that is, assessment, discussion, and active management.[68]

Survey results, Kunzel reported, indicated that general dentists are more willing to manage the care of diabetic patients on an assessing/advising basis than on a more active management basis.[68] With respect to periodontists, it was found that this pattern of active involvement with diabetic patients continued, although overall periodontists performed active management behaviors more frequently than general dentists.[69] Kunzel explained that when assessed internationally in a representative sample of general dentists in New Zealand, this pattern of involvement with the diabetic patient was again found. Most general dentists in New Zealand, she explained, participated in the assessment and discussion phases of managing patients with diabetes, but the prevalence of involvement in active management activities was lower.[70]

From an attitudinal perspective, Kunzel reported that the survey results showed that general dentists did not feel that they had mastery of the knowledge or behavioral areas involved; that viewing such activities as peripheral loomed as a barrier to performing them; and that they did not believe that their colleagues or patients expected them to perform such activities.[68] Like general dentists in New Zealand, Kunzel explained, over half of US general dentists viewed more active management of patients with diabetes as the responsibility of others. Also, more than half, like those in New Zealand, believed that taking an active role in diabetes management was useful, but only about half that percentage thought it was easy. A minority in both the US and in New Zealand believed that their colleagues expected them to take a more active role in diabetes management.[70] Periodontists' attitudes were not clearly different than those of their general dentist colleagues.[69]

When dentists were asked about their willingness to perform certain active management activities, the results, Kunzel reported, varied depending on the activity involved. When dentists were asked about their willingness to screen for diabetes with a finger-stick test, relatively low levels of willingness were indicated. Kunzel suggested that these low levels may reflect concern over regulatory issues regarding the use of the test. Or they may reflect dentists' reluctance to prick fingers to obtain a blood sample. Survey results, Kunzel reported also showed that over 85% of periodontists expressed strong willingness to refer a patient for such an evaluation which, Kunzel proposed, suggests substantial inclination on

their part to screen patients for undiagnosed diabetes, while a more moderate, but substantial, 69% of general dentists also expressed strong willingness do so.[70]

To further their understanding of how to encourage more involvement in active management, Kunzel explained that she and her colleagues developed predictive models to identify explanators remove highlight of general dentists' and periodontists' active management of the diabetic patient.[71] They found that general dentists were more influenced by the nature of their relationship with, and the characteristics of, their patients, while periodontists were more influenced by the nature of their relationship with their colleagues.

Kunzel concluded her presentation by posing a rhetorical question. She asked, "Dare we be optimistic that the percentages of dentists, both general and specialist, who adopt more active management for the diabetic patient, will grow in the future?" Her response, showed some optimism. Kunzel pointed out that in New Zealand younger dentists seem to believe that their colleagues expect them to take a more active role in diabetes management.[70] This difference, Kunzel suggested, may reflect changes in the dental curriculum over time; perhaps, she proposed, there is more understanding of the general-oral health connection present in the curriculum. As for the US, Kunzel pointed out that there were indications that periodontists can play a leadership role in adoption efforts, since they, in higher percentages, are involved in active management of the diabetic patient.[69] Also suggested, is the adoption of an incremental approach in which clinicians are first encouraged to become more actively engaged in discussion with the patient because for those who actively discuss they tend to actively manage their diabetic patients.[71] It is hoped, Kunzel explained, that such understandings, along with others, can contribute to diminishing a possible gap between the growth of science and the adoption of practice in this realm of patient care.

In her presentation titled "Working Across Medical-Dental Professional Boundaries in the Management of Diabetes and its Complications", Pamela Allweiss, MD, MPH (Centers for Disease Control and Prevention; University of Kentucky College of Public Health) presented examples of how medical and dental professionals can work together as a team to care for people with diabetes and on the resources in the public domain that help this partnership.

Allweiss began her presentation by first giving the key points of consideration of the medical and dental professionals partnership. The points included: (a) coordination of care presents many challenges when delivered by multiple providers in a variety of settings; (b) coordination will help ensure adherence to the intended treatment plan and identify drug and disease management problems in a timely manner; and (c) dental care professionals are often a primary point of care for people with diabetes.

Allweiss explained that the need for team care for people with diabetes that includes dental professionals and other health care professionals such as pharmacists, podiatrists, and optometrists is already being addressed by the National Diabetes Education Program (NDEP), a joint initiative of the Centers for Disease Control and Prevention (CDC) and the National institutes of Health (NIH). NDEP, which partners under the umbrella of the PPOD (pharmacists, podiatrists, optometrists, and dentists) has over 200 public and private partners from multiple sectors (public health, health systems, community programs especially targeting populations with a large burden of diabetes) and is involved in the development and dissemination of evidence based, focused group tested materials that include diabetes control and prevention messages.

Two resources created by the NDEP include the PPOD Primer tool and the PPOD Checklist. Allweiss described each. The PPOD Primer tool (Fig. 3) was developed to educate multiple

providers to focus on comprehensive, interdisciplinary diabetes care. The tool includes sections that are specific to each discipline and are designed to provide a quick "crash course" on each specialty and its relation to diabetes. Each section is written for the "other" providers to read and focuses on educating each provider about the role the other professions play in the diabetes care team. Emphasis is placed on the importance of conducting routine exams for complication prevention, recognizing danger signs, making recommendations regarding referrals, reinforcing among patients the need for self-exams, and of course, the importance of metabolic control. The goal of the PPOD Primer tool is to provide consistent messages across the disciplines and to encourage collaboration and a team approach in the caring for people with diabetes.

The PPOD Primer tool, Allweiss continued, also has a patient education component. The tool informs patients that periodontal infection may make it difficult to control diabetes and conversely, that poor metabolic control may increase susceptibility to infection. In addition, it explains that patients who have diabetes may be more likely to get periodontal infections, that the infection may take longer to heal, and that untreated infection may lead to loss of teeth. The PPOD Primer tool is widely disseminated via a variety of methods. Some of those include distribution at professional meetings, continuing education programs, by professional associations and it is also available on the NDEP website and at the NDIC Clearinghouse

The PPOD Checklist, Allweiss explained, is a tool developed by PPOD Providers and other health care professionals such as physicians, physicians' assistants and nurses. Its goals are to ease communication among multiple providers, educate people with diabetes about needed exams, and help to improve pay for performance measures. During the development of the "Checklist" the PPOD working group conducted a pilot test of a Multidisciplinary Patient Care Checklist. Individual working group members sent the checklist to co-workers and colleagues, and invited them to comment via an online Survey Monkey questionnaire. The goal of the pilot was to gauge whether the checklist would be useful, and used, in a real-world clinical setting. Most respondents agreed the content was appropriate and presented clearly. In addition, 74.3% responded that they were likely to change their practice to more of a team approach, incorporating the members of the team, or by referral. In closing, Allweiss reported that the survey responses revealed that the checklist is useful in actual practice, with many (30%) indicating its potential application in EMR/EHR systems. It is currently being pilot tested in an electronic Medical Records format and will eventually be available on the NDEP web site.

Conclusion

The 2011 New York Academy of Sciences conference on diabetes and oral disease brought together clinicians and researchers from medicine and dentistry, and provided a setting for education and interaction aiming to increase awareness and collaboration across disciplines. Conference speakers covered information on the demographics, epidemiology, pathophysiology and treatment of diabetes and periodontitis. They explained the factors that constitute the bidirectional diabetes-oral disease link and defined the role of oral disease in initiating the inflammatory response, as well as the impact of hyperglycemia on oral health. In addition, speakers presented information on how to screen and counsel patients for oral disease and diabetes risk and emphasized that inter-professional patient management is essential in order to achieve improved health outcomes in affected individuals.

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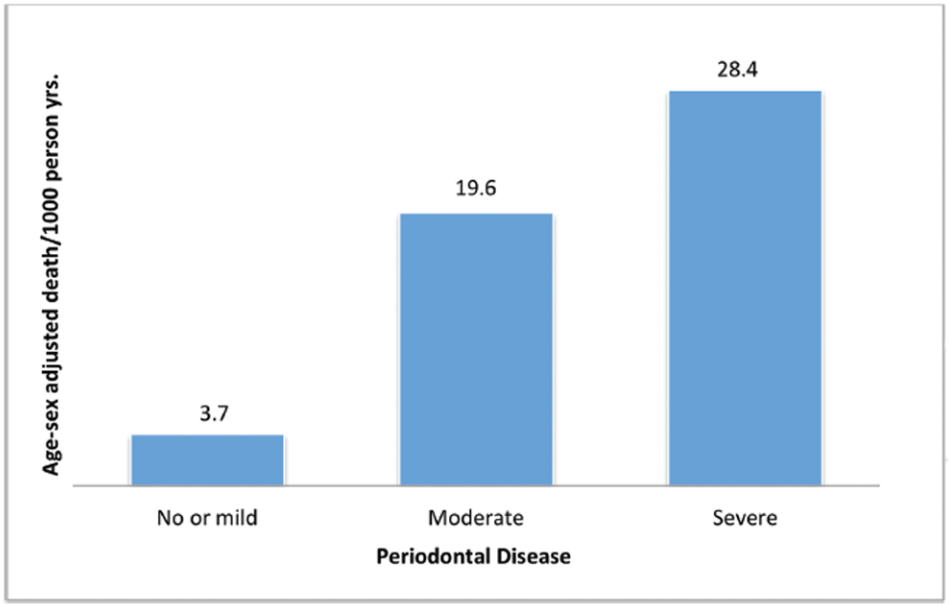

Figure 1.
Mortality rates (all natural causes) in diabetic patients by periodontal disease status adjusted for age and sex to the 1985 Pima Indian population. Adapted from Saremi *et al.*[3]

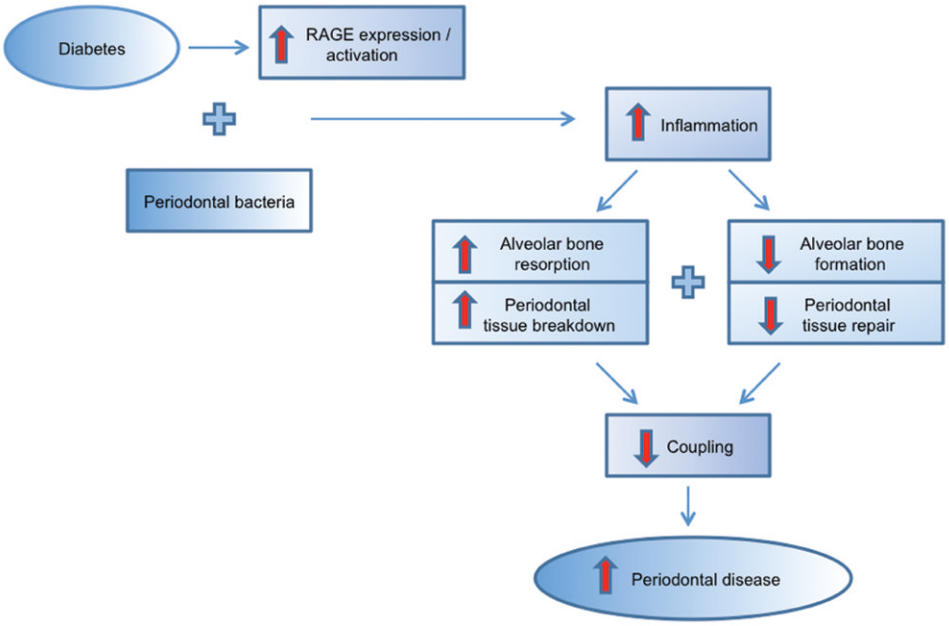

Figure 2.
A model for the pathogenesis of enhanced periodontal disease in diabetes. Abbreviation: RAGE, receptor for advanced glycation endproducts

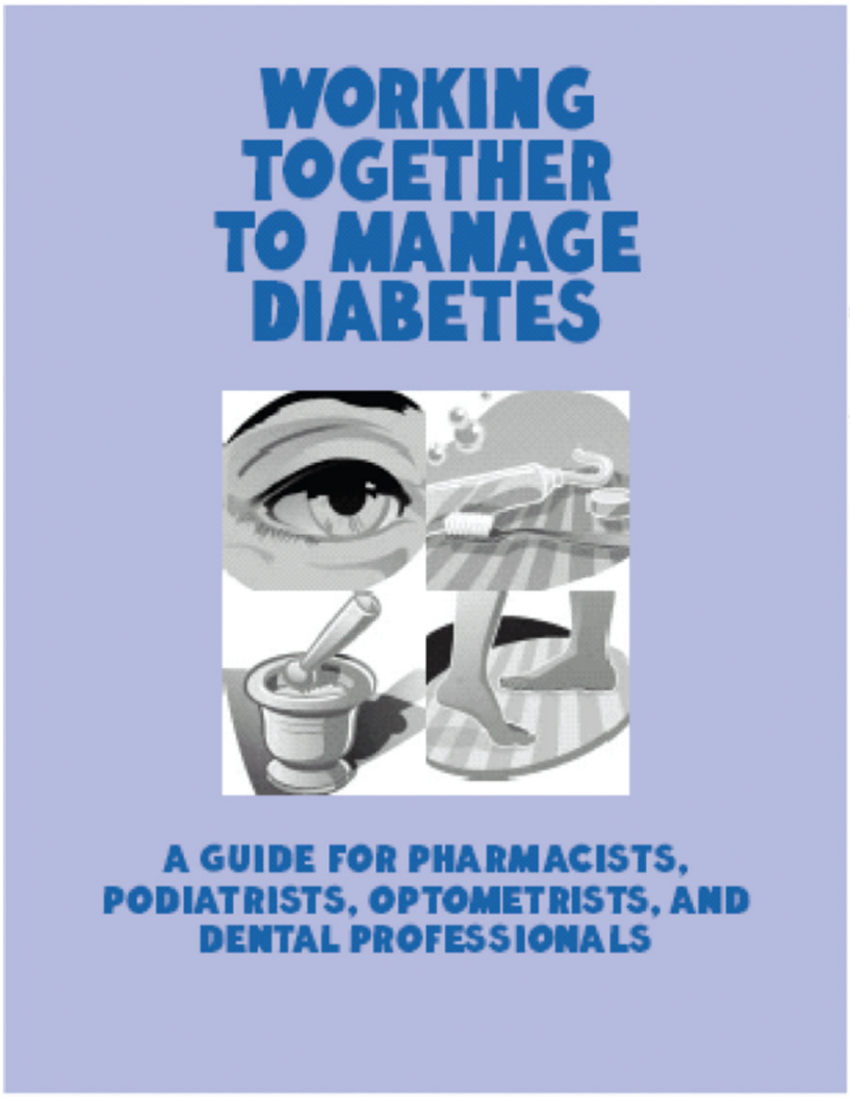

Figure 3.
The National Diabetes Education Program (a joint initiative of the Centers for Disease Control and Prevention and the National Institutes of Health) primer tool created to promote proper diabetes management by pharmacists, podiatrists, optometrists, and dentists.

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Table 1

Effect of non-surgical periodontal treatment on HbA1c levels in diabetes (meta-analysis of five studies, adapted from Teeuw *et al.*[15]) Weighted mean difference (WMD) of baseline (B) to end (E) in% HbA1c between treatment (Tx) and control (C) groups.

	Tx Diff HbA1c B–E		C Diff HbA1c B–E			
Study	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**Weight %**	**WMD 95% CI**
Katagiri 2009	32	−0.14 (0.63)	17	−0.09 (0.57)	27.42	−0.05[−0.40, 0.30]
Jones 2007	74	−0.65 (1.21)	80	−0.49 (1.22)	26.03	−0.16[−0.54, 0.22]
Kiran 2005	22	−0.86 (0.77)	22	0.31 (1.83)	12.77	−1.17[−2.00, −0.34]
Promsudthi 2005	27	−0.19 (0.74)	25	0.12 (1.05)	21.84	−0.31[−0.81, 0.19]
Stewart 2001	36	−1.90 (1.93)	36	−0.80 (1.85)	11.94	−1.10[−1.97, −0.23]
Total	191		180		100	−0.40[−0.77, −0.04]

Heterogeneity between 5 studies was 59.5%; test for heterogeneity: $Chi^2 = 9.87$, df = 4, $P = 0.04$ Test for overall effect: $Z = 2.15$, $P = 0.03$