Workshop on Oral Diseases and Diabetes

Embassy Suites Hotel
Chevy Chase - Washington, D.C.
December 6 and 7, 1999

Co-Chairs:

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Columbia University

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State University of New York at Buffalo

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Introduction

The National Institute of Dental and Craniofacial Research (NIDCR) is very pleased to sponsor this workshop on the oral complications and associations with insulin-dependent diabetes mellitus. It is estimated that more than 10 million Americans suffer from diabetes, and another six million people are yet to be diagnosed. With our nation's changing demographics and changing patterns of disease, diabetes is particularly important to the health and well-being of a very significant number of people. In addition, we are realizing that diabetes is a type of autoimmune disease that involves complex associations and interactions between disparate metabolic activities such as glycolysis and lipogenesis. We further understand that oral infections can exacerbate diabetes, and that diabetes induces multiple oral complications. Therefore, it is imperative that NIDCR, NIDDK and other NIH Institutes, Centers and Offices collaborate on in this complex human disease, and take the opportunity to use your recommendations to accelerate scientific progress to understand and eventually reduce the burden of diabetes.

Harold Slavkin, D.D.S.
Director, National Institute of Dental and Craniofacial Research, NIH

Workshop Objectives:
To review the current state-of-the-science in research on the major oral complications associated with diabetes mellitus. To explore areas that are not receiving adequate attention and support. To envision new avenues of research, especially clinical studies and interventions, that will accelerate transfer of data from the laboratory to the clinic.

EXECUTIVE SUMMARY OF WORKSHOP

Diabetes mellitus is a serious metabolic condition that affects as many as 16 million Americans (i.e., approximately 6 % of the population.) A major problem in treating and diagnosing diabetes is that about half to these individuals are unaware that they have the disease. Current treatments require substantial involvement of the patient, and thus, individuals who are unaware that they have the disease do not take action until complications develop. In addition to diseases of the eye, kidneys, heart, nerves and blood vessels, oral complications are a major complication of diabetes. Oral complications include periodontitis (gum disease), salivary dysfunction, mucosal infections, and neurological problems of taste and smell. The prevention, diagnosis and treatment of these infections are central responsibilities of oral health care practitioners in the overall management of diabetes mellitus. Research and support for research on these complications is a major part of the mission of the NIDCR. All major administrative components of NIDCR, including the Division of Intramural Research, Division of Extramural Research, and the Office of the Director, are involved in meeting this mission of improving oral health in the diabetic patient.

The Workshop on Oral Diseases and Diabetes was designed to serve as a forum for evaluation of the current state-of-the-science on diabetes and oral health, as well as to develop a working list of recommendations for future research on this topic. The recommendations are intended to be a basis for new research efforts by the NIDCR to prevent, treat, diagnose and cure oral complications of diabetes mellitus. Public comment on these recommendations, and submission of additional recommendations is encouraged.

RECOMMENDATIONS FOR FUTURE RESEARCH

Throughout the meeting, participants were asked to provide recommendations for future research based on their own experience, what colleagues had told them, and the information they learned at the workshop. Listed below are the recommendations that were received for the 13 major topics covered during the workshop.

I. General

The complications associated with diabetes must be studied in patients with various forms of diabetes. In general, studies must include evaluation of the oral complications of both Type 1 and Type 2 diabetes, and encourage the development and use of novel animal models (genetically characterized mice, SCID mice, gene knockout mice), particularly genetic models of Type 2 diabetes.

II. Infectious Diseases

Oral infections, particularly periodontal diseases, are major complications of diabetes. Therefore, a large part of the meeting was devoted to this topic. Recommendations included a longitudinal study that thoroughly compares, using state-of-the-science

techniques, the bacteria and immune response to these bacteria in diabetics and healthy individuals (or well-controlled diabetic patients).

III. Inflammation and Immunity

Inflammation and immune responses are negatively influenced by diabetes. Clearly, the host response to exposure to foreign microbes and to the healing process needs further clarification. Recommendations were to evaluate the entire (cellular, antibody, and innate) mucosal immune capacity of the diabetic patient, including salivary gland function.

IV. Bone & Connective Tissue

A devastating complication of diabetes is the loss of bone and connective tissue associated with the oral cavity. This seems to be an advanced area of research that could benefit greatly from additional research. There was a strong call for study of the pathogenesis of bone loss in diabetic animals.

V. Vascular Disease

The periodontium contains highly vascularized tissues. Since diabetes has profound effects on the microvasculature, the effects of diabetes on the gingival tissues could be great. The oral cavity provides an unparalleled opportunity to examine and follow the pathogenesis of vascular diseases in situ. Recommendations include studies on the source and characteristics of growth factors involved in vascular diseases and vascular hyper-permeability in the diabetic patient.

VI. Neuropathy

Another oral complication of diabetes is alterations in taste sensation and burning mouth. Additional studies are needed to evaluate and characterize taste, smell, and oral pain in diabetic patients.

VII. Genetics

Both diabetes and periodontitis appear to be genetically complex diseases. Recent studies and new techniques are providing insight into the involvement of genes in both of these diseases. Recommendations include studies on the genetic relationships between diabetes and periodontitis, evaluation of individual genetic differences in responses to diabetes, and studies on the genetics of inflammatory mediators important to diabetic complications.

VIII. Saliva and Salivary Glands

Changes in salivary composition and salivary dysfunction are frequent complications of diabetes. Because the role of saliva is so critical to oral health, more research is needed on this topic. Recommendations include characterizing the changes in saliva and salivary tissue

(both major and minor salivary glands) in diabetic patients and animal models. Also, determine whether saliva can be used as a noninvasive marker of diabetes and glycemic control.

IX. Behavior

The workshop attendees considered behavior to be an integral part of both the cause and solution to oral complications of diabetes. The importance of the patient in oral health care and treatment of diabetes is thus crucial to all health care measures to prevent and treat the oral complications of diabetes.

X. Systemic Diseases:

Diabetic complications in the oral cavity may be related to those found in various other body locations. The relationship between disease in one part of the body appears to be intricately tied to disease in other parts of the body. Thus, treatment of one complication might have a beneficial influence on other complications. Similarly, as a logical, yet unproven, extension of the Diabetes Control and Complications Trial results, metabolic control of diabetes could have beneficial effects on all complications, including those in the oral cavity. Attendees urged for more research on the connections between periodontitis and other diabetic complications (e.g., retinopathy, nephropathy).

XI. Clinical Studies:

The need for new and well designed clinical studies to evaluate the associations between oral complications and diabetes was articulated by many of the participants as the number one priority issue. More research is needed to determine the effect of treatment of oral infections on glycemic control, oral complications in the elderly diabetic patient, and whether lipid-lowering therapies have a beneficial effect on the complications associated with diabetes, periodontitis, and other chronic inflammatory diseases.

XII. Translation Research:

Information learned from animal models can be used, for example, to design better therapeutic agents and randomized clinical trials in human. The workshop experts agreed that translation and disseminate information about the bi-directional relationship between diabetes and periodontal disease into the knowledge-base and clinical practices of non-dental health care providers is sorely needed. Finally, study whether the dental office is a feasible site to identify patients.

XIII. Administration

Establish a NIDCR "Scout Group" to search for opportunities to include oral sub-studies in large diabetes and obesity studies.

Co-Chairs: A. Schmidt, R. Genco, A. Notkins, D. Mangan

Monday, December 6

7:30 – 8:00 a.m.   **Registration**

8:00 – 8:15   **Welcome and Workshop Objectives**
                 Moderator: Dennis Mangan, NIDCR
                 Harold Slavkin, Director, NIDCR
                 Allen Spiegel, Director, NIDDK

SESSION I - Overviews of Diabetes
                 Moderator: Abner L. Notkins, NIDCR

8:15   **Epidemiology and Financial Impact**
                 Maureen Harris, NIDDK

8:35   **Etiology and Pathogenesis of IDDM (type 1)**
                 Ake Lernmark, University of Washington

8:55   **Etiology and Pathogenesis of NIDDM (type 2)**
                 Jesse Roth, John Hopkins University

9:15   **Long-term Complications**
                 Michael Brownlee, Albert Einstein

9:35   **Genetics**
                 Soumitra Ghosh, Children's Hospital of Wisconsin

9:55   *BREAK*

10:15   **Therapy**
                 Lester Salans, Rockefeller University

SESSION II - Effects of Diabetes on Periodontitis
                 Moderator: Robert Genco, SUNY at Buffalo

10:30   **Diabetes and Periodontitis**
                 Robert Genco, SUNY at Buffalo

10:45   **Periodontal Disease in Type 2 Diabetes:**

US Population, 1988-94
Rob Selwitz, NIDCR

11:00	**Genetics of Periodontitis** Thomas Hart, University of Pittsburgh
11:15	**Destruction of Connective Tissue** Larry Golub, SUNY at Stony Brook
11:30	*DISCUSSION*

KEYNOTE ADDRESS: **Bone Regeneration**
11:45   Hari A. Reddi, University of California – Davis

12:10 p.m.   *LUNCH BREAK* (on your own)

KEYNOTE ADDRESS: **The Inflammatory Response**
1:05   Peter Ward, University of Michigan

SESSION III - Effect of Periodontitis on the Control of Diabetes
      Moderator: George Taylor

1:30	**Periodontitis and Systemic Disease** David Paquette, University of North Carolina
1:45	**Diabetes Control, Periodontal Health** George Taylor, University of Michigan
2:00	**Treatment of Periodontitis in Pima Indians** Sara Grossi, SUNY at Buffalo
2:15	*DISCUSSION*
2:30	*BREAK*

SESSION IV – Pathogenesis and Wound Healing
      Moderator: Ann Marie Schmidt

2:45	**Advanced Glycation Endproducts and theirs Receptors** Ann Marie Schmidt, Columbia

3:00   **The Role of Serum Lipids and Microphage Function in**
Wound Healing

      Anthony Iacopino, Marquette University

3:15   **Matrix Metalloproteinases**

Maria Ryan, SUNY at Stony Brook

3:30   *DISCUSSION*

KEYNOTE ADDRESS: **Bacterial Infection**
3:45   Sam Baron, University of Texas at Galveston

4:10   *BREAK*

SESSION V - Infections
           Moderator: Sam Baron

4:30   **Microbial Considerations in Diabetes**
           Sigmund Socransky, Forsyth Dental Institute

4:45   **Periapical Lesions in NOD Mice**
           Ashraf F. Fouad, University of Connecticut

5:00   **Infections and Insulin Resistance**
           Charles H. Lang, Pennsylvania State University Medical

Center

5:15   *DISCUSSION*

Tuesday, December 7

7:30 – 8:00 a.m.   **Registration**

SESSION VI - Salivary Function
           Moderator: Leigh C. Anderson

8:00   **Hormonal Regulation of Salivary Gland in Diabetes**
           Leigh C. Anderson, University of Washington

8:15   **Salivary Gland Dysfunction in Autoimmune NOD Mice**
           Ammon Peck, University of Florida

8:30   **Regulation of Autoimmunity in the NOD Mouse**
           Ava J. Wu, Stanford University

8:45   *DISCUSSION*

SESSION VII - Oral Health Care
           Moderator: Jonathan Ship

| 9:00 | **Oral Health and Diabetes** |
| | Alex White, Kaiser Permanent |

| 9:15 | **Oral Health and Glycemic Control in Older Diabetics** |
| | Jonathan Ship, University of Michigan |

| 9:30 | *DISCUSSION* |

| 9:45 | *BREAK* |

SESSION VIII   - Current Support of Diabetes Research at NIDCR
10:00   Dennis Mangan, NIDCR

SESSION XI - Future Research Directions: Basic and Clinical Priorities

10:15	**Round Table I:**
	Basic Research
	Moderators: Robert Genco and Ann Marie Schmidt

| 11:45 | *LUNCH BREAK* (on your own) |

1:00	**Round Table II:**
	Clinical Research
	Moderators: Maria Ryan and Ira Lamster

SESSION X - Preparation of Workshop Report
2:30   Moderators and Co-Chairs

Abstracts of Presentations

Epidemiology, Scope, and Impact of Diabetes

Maureen I. Harris, PhD, MPH
National Institute of Diabetes and Digestive and Kidney Diseases, NIH

The scope and impact of diabetes mellitus in the United States has grown rapidly in the past 30 years. Over 11 million people are now known to have diabetes, and an additional 5 million meet diagnostic criteria for diabetes but remain undiagnosed. Further, about 13 million people have impaired fasting glucose, a condition in which blood glucose levels are not diabetic but are clearly greater than normal and which conveys high risk for subsequent development of diabetes. Minority populations have higher rates of diabetes, compared with the majority white population, and comprise 25% of all patients with diabetes. Prevalence rates among African Americans and Mexican Americans are 2 to 3 times those of non-Hispanic whites, and rates among Native Americans are 2 to 5 times higher.

Diabetes causes substantial morbidity and premature mortality in the United States. It is the leading cause of new cases of blindness, the leading cause of end-stage renal disease, and the leading cause of nontraumatic lower extremity amputation. Each year, one in 400 diabetic patients develops renal failure and one in 150 patients has an amputation. Life expectancy for patients with these end-stage complications is only about 3-4 years. Neuropathy is present in 60%-70% of patients, although most of the neuropathy is subclinical. Mortality for patients with diabetes is 2-4 times that of nondiabetic patients. The cost for medical care of diabetes in the U.S. is about $95 billion annually. This translates to over $11,000 per patient per year, which is three times the cost for a nondiabetic patient.

Although all patients with diabetes are at high risk for microvascular and macrovascular complications, minorities are more likely to develop the microvascular complications of diabetes and to have lower extremity amputations, although their rates of coronary heart disease are lower than in non-Hispanic whites.

Undoubtedly, high blood glucose levels are the major reason for diabetic microvascular complications. Glycemic control is not optimal in the United States. Although about 80% of patients with type 2 diabetes are treated with insulin or oral agents, their average fasting plasma glucose is over 200 mg/dl and the average post-prandial value is over 300 mg/dl. Fully 58% have HbA1c values greater than 7%, a value that is 5 standard deviations above the mean for a nondiabetic population. The Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes clearly showed that diabetic complications can be markedly reduced by better glycemic control. Diabetic patients also have high rates of obesity, hypertension, and dyslipidemia which are major reasons for their 2-4 fold higher rates of cardiovascular disease. These high rates of risk factors and adverse outcomes occur despite the fact that patients appear to have adequate health care access and financial coverage for medical care.

Etiology and Pathogenesis of Type 1 (IDDM) Diabetes

Åke Lernmark
University of Washington
Seattle, Washington

Type 1 (insulin-dependent) diabetes is related to autoimmune phenomena directed against the pancreatic islet beta cells. The genetic susceptibility is strongly associated with HLA-DQ and DR on chromosome 6, but genetic factors on other chromosomes such as the insulin gene on chromosome 11 and the CTLA-4 gene on chromosome 2 may modulate disease risk. The environmental etiological factors are complex and no single agent have been identified. Gestational infections may contribute to initiation while later infections may accelerate islet beta cell autoimmunity. The pathogenesis is associated with autoimmunity against the islet beta cells. Insulitis is often but not always seen at the time of clinical diagnosis, which seem to occur when 80-90% of the beta cells have been destroyed. The rate of beta cell destruction is related to both HLA and the presence of autoantibodies against GAD65, insulin or I-A2, a tyrosine phosphatase-like protein. Molecular techniques are used to establish reproducible and precise autoantibody assays, which have been subject to worldwide standardization. The diagnostic sensitivity and specificity of all three autoantibodies for Type 1 diabetes are high and double or triple positivity among first-degree relatives predicts disease. Combined genetic and antibody testing improved prediction in the general population. Classification of diabetes has also improved by autoantibody testing and may be used in type 2 diabetes to predict secondary failure and insulin requirement. Islet cell autoantibodies may be related to late complications including periodontitis, perhaps because the presence of islet cell autoantibodies marks different residual beta cell function. The autoimmune character of Type 1 diabetes makes it important to take immunogenetic factors into account when studying oral complications associated with diabetes.

Type 2 Diabetes

Jesse Roth, MD, FACP

The incidence of Type 2 diabetes (T2DM) is rising in the United States and worldwide in the wake of an epidemic of obesity. The genetic foundations of diabetes and of obesity are just beginning to be uncovered including single genes (recessive, dominant, and dominant negative); susceptibility genes that act in concert with the environment and time; and defects in mitochondrial DNA.

Early in Type 2 diabetes, insulin resistance is associated with hyperinsulinemia. Later the decline of insulin secretion plays an increasingly important role. Recent studies also show that a significant minority of adults who appear to have Type 2 diabetes actually have late onset, slowly progressing autoimmune Type 1 diabetes who progress to beta cell loss, insulin deficiency, and dependence on insulin therapy.

Glucose and free fatty acids, in addition to being metabolic fuels, act as signaling agents and, in excess as toxins. They act in concert with other molecular signals to create the pathophysiology. Our understanding of the fat cell has evolved progressively from an inert mass to a metabolically active tissue, to a highly active secretory system, which may also progress to metastatic storage of fat in a wide range of nonadipose tissues. These studies help relate epidemiological and clinical studies of obesity to mechanisms of insulin resistance and the diabetogenic effects of obesity.

The UKPDS study published in 1998 has documented that the natural history of Type 2 diabetes is a progressive decline in glucose metabolism. Aggressive treatment aimed at the blood glucose and the blood pressure yield better outcomes than traditional approaches, but normalization of glucose and of blood pressure remain elusive goals with the currently available tools. Multiple drugs are being developed with specific molecular targets.

Long-Term Complications

Michael Brownlee, MD
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Albert Einstein College of Medicine
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Diabetes is the leading cause of blindness, renal failure, limb amputation and myocardial infarction in the US. Hyperglycemia is the proximate cause of damage to microvessels, nerves, and arteries, although genetic factors influence complications susceptibility. Only cells that develop intracellular hyperglycemia are damaged by diabetes. Major mechanisms include increased aldose reductase pathway activity, increased protein kinase C activity, and increased intracellular formation of precursors of advanced glycation endproducts.

Genetics of Diabetes

Dr. Soumitra Ghosh
Medical College of Wisconsin

Diabetes represents a paradigm for the genetics of complex disease. There are multiple genes and environmental factors which determine disease susceptibility. Both positional cloning and candidate gene approaches have been attempted but only a few genes identified. Candidate gene studies have yielded disease-associated polymorphisms in the HLA and insulin gene regions for type 1 diabetes, whereas positional cloning has been successful in maturity onset diabetes of the young, a rare form of type 2 diabetes with an earlier age of onset, autosomal dominant mode of inheritance and beta cell dysfunction. Positional cloning has also identified numerous other chromosomal regions harboring putative susceptibility genes, but progress has been hampered by (a) the general lack of power or resolution and the difficulty faced in analyses which incorporate multiple loci and gene-environmental interaction; (b) inconsistent results from different studies; (c) the paucity of markers for use in fine mapping and (d) the presence of other factors besides recombination which determine the efficiency of high-resolution genetic mapping. Mapping methods should always be complemented by functional studies and it is now possible to study large-scale gene and protein expression in specific tissues. Finally, with the recent deluge in human genome sequence information and the increasing availability of single nucleotide polymorphisms, there is renewed enthusiasm that positional cloning will yield novel molecules as targets for strategic intervention in the prevention and therapy of diabetes.

Treatment of Diabetes Mellitus

Lester B. Salans, M.D.
The Rockefeller University and Mt. Sinai School of Medicine
New York, New York

The major components of management of diabetes mellitus include treatment of hyperglycemia to target levels (FPG < 7 mmol/l, HbA1c ≤ 7%), maintenance of normal plasma lipid levels, control of hypertension, achievement and maintenance of normal body weight, management of diabetic complications, patient education and institution of a self care-program. Traditionally and currently, assessment of treatment efficacy relies on measurement of FPG and HbA1c.

Current treatment and treatment approaches are unsatisfactory. Target levels of glycemic control are too often not achieved, especially over the long run. Chronic complications of diabetes continue to develop. In most patients, the severity of disease progresses in over time. Many factors contribute to this unacceptable situation, including limited understanding of the underlying etio-pathogenesis of diabetes, unphysiologic replacement of insulin by injection or mechanical device, insufficient efficacy of individual oral hypoglycemic agents, and stringent therapeutic regimens for achieving target glycemic levels that so impair quality-of-life and cause such frequent severe hypoglycemia and other side effects that many individuals become treatment non-compliant.

In Type 2 diabetes, the focus of this presentation, treatment is too late, too little and too narrowly focused. Diagnosis and treatment of Type 2 disease begins too late in the course of the disease, is not targeted to early potentially modifiable abnormalities, often does not address the major known pathophysiologies of the disease, and is too narrow in its focus on control of fasting blood glucose and HbA1c. In addition to the need for more effective and safe oral hypoglycemic agents, a "paradigm shift" in the approach to treatment of Type 2 diabetes is needed.

One of the earliest detectable abnormalities in the course of development of Type 2 diabetes is altered kinetics of insulin secretion. Loss of early/first phase insulin secretion leads to mealtime and post-meal hyperglycemia, the earliest clinical stage of Type 2 diabetes and the characteristic feature of impaired glucose tolerance (IGT). Mealtime hyperglycemia alters the metabolic milieu leading to loss of normal glucose and lipid homeostasis, fasting hyperglycemia and increased 24-hour exposure to excess glucose, hyperinsulinemia, and other metabolic abnormalities that contribute to the development and progression of micro- and macrovascular complications. Numerous epidemiological studies demonstrate that *mealtime and post-meal hyperglycemia are independent risk factors for cardiovascular disease (CVD)*, the complication primarily responsible for most diabetes mortality. They appear to be more predictive of CVD risk than fasting hyperglycemia.

More successful treatment of Type 2 diabetes in the future will require earlier diagnosis and early treatment, treatment with agents that are targeted to early, potentially modifiable abnormalities such as loss of early insulin secretion and mealtime/post-meal hyperglycemia, greater and earlier use of combination therapy, and "tighter" control of dsylipidemia and hypertension.

Diabetes and Periodontitis

Robert J. Genco, D.D.S., Ph.D.
Department of Oral Biology
School of Dental Medicine
SUNY at Buffalo

The evidence for type 2 diabetes as a risk factor for periodontal disease is extensive. The evidence consists of cross-sectional, longitudinal, and epidemiologic studies. There is also support for the role of diabetes in periodontal disease from animal model studies and *in vitro* studies of mechanisms. Evidence for the role of type 1 diabetes as a risk factor for periodontal disease is less extensive, consisting mainly of cross-sectional studies.

The role of periodontal infection in reducing glycemic control in diabetics has recently been elucidated by longitudinal epidemiologic studies in which severe periodontitis is associated with poor glycemic control, and by randomized controlled trials in which periodontal therapy reduced glycated hemoglobin levels. The mechanism for the effect of periodontal infection on glycemic control in diabetics is not clear, however, infection may contribute to insulin resistance, possibly through bacterial effects on post-insulin receptor mechanisms affecting signal transduction. Studies are needed to elucidate the detailed mechanisms by which alterations in diabetes mellitus increase the risk for periodontal infection, as well as the mechanisms by which periodontal infections in diabetics lead to altered glycemic control. Further studies are also needed to determine if management of periodontal disease will reduce other complications of diabetes mellitus.

Periodontal Disease in Diagnosed Type 2 Diabetes: U.S. Population, 1988-94

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[2]University of Bergen, Norway

Diabetes is a known risk factor for periodontal disease; however, there has been little information in the literature describing periodontal disease and diabetes in nationally representative population studies. This report describes the prevalence and extent of selected periodontal conditions in previously diagnosed Type 2 diabetics (PDMs), as compared to persons not having diagnosed diabetes (NDMs). A national sample of 9,600+ dentate adults aged 30 years and over, representing about 105 million Americans, received a periodontal examination during NHANES III. Trained and calibrated examiners assessed periodontal disease at mesiobuccal and mid-buccal tooth sites of fully erupted permanent teeth present in two randomly selected quadrants, one maxillary and one mandibular, using standardized NIDCR criteria. Diabetes diagnosis status was determined via interviewer-administered questionnaire. Statistical analyses were conducted with weighted data using SUDAAN and STATA software. Higher percentages of PDMs had one or more sites with: loss of attachment ≥5 mm (LOA), probing pocket depth ≥5 mm (PPD), gingival bleeding (GB), recession ≥3 mm (REC), presence of both supra- & subgingival calculus (SSC), or presence of subgingival calculus only (SC) than did NDMs (for all comparisons, $p < 0.05$; age and gender controlled). In addition, PDMs on average had higher percentages of teeth having one or more sites with: LOA, PPD, GB, REC, SSC, and SC (for all comparisons, $p < 0.05$; age and gender controlled). PDMs were more likely to have LOA (odds ratio = 1.5), PPD (2.1), GB (1.5), and SSC (2.1) than were NDMs (for all comparisons, $p < 0.05$; age, gender, and race ethnicity controlled). As compared to NDMs, the prevalence and extent of periodontal conditions in PDMs generally were higher for both males and females and for non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. Conclusion: Periodontal disease in the U.S. adult population is more prevalent and more extensive in diagnosed Type 2 diabetics as compared with adults not having been diagnosed as diabetic.

Genetics of Periodontal Diseases

Tom Hart, DDS, PhD
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Both type 1 and type 2 diabetes mellitus are associated with increased periodontal disease susceptibility. Advanced periodontitis is reported to be associated with impairment of metabolic control in both groups. Although altered host inflammatory response are believed to play an important role in diabetes-associated periodontitis, it is unclear whether this increased risk for periodontitis results from the primary defect that causes diabetes, or occurs as a sequellae of systemic effects of the diabetic state. Understanding the genetic basis of periodontitis susceptibility and pathobiology should help us to understand the interplay of diabetes and periodontitis.   Periodontal disease are a heterogeneous group of conditions. While some early onset forms of disease are caused by genes of major effect, adult forms appear to be genetically complex. Strategies to identify the genetic basis of these diseases will include genetic approaches to study both simple genetic diseases as well as complex genetic diseases.

Diabetes Induced Destruction of Periodontal Connective Tissues.

Lorne M. Golub and Maria E. Ryan, Dept of Oral Biology & Pathology, School of Dental Med., SUNY at Stony Brook, NY

Collagen (particularly types I and III) is the major structural protein of the gingiva periodontal ligament, and organic matrix of the alveolar bone and its disorganization and destruction are key events in diabetes-enhanced periodontal diseases. Elevated production and activity of host-derived collagenases (particularly MMP-8 generated by cytokine-stimulated fibroblasts as well as leukocytes), which mediate collagen breakdown extracellularly as well as intracellular alterations such as decreased expression and increased degradation of procollagen, contribute to gingival connective tissue destruction during experimental insulin-deficient diabetes. Although accelerated alveolar bone loss clearly occurs in experimental diabetes, it is less clear that this reflects enhanced osteoclast (& MMP) – mediated bone formation may be more important as they are in diabetes-induced skeletal bone loss (osteoporosis). The relationships between (i) these alterations in collagen metabolism, (ii) non-enzymatic glycosylation of tissue and serum proteins, and (iii) the beneficial protein of non antimicrobial tetracycline analogs, will be discussed.

Bone Regeneration: Implications for Oral Complications of Diabetes

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It is well known that repair and regeneration of several tissues including bone is impaired in Diabetes. Most oral biologists are familiar with oral and periodontal complications of Diabetes. The recent progress in the isolation and cloning of signals for bone differentiation, their cognate receptors, intracellular substrates for receptor kinases and their genomic targets has set the stage for translational research to improve and accelerate repair of bone, periodontal ligament and cementum.   My talk will focus on bone morphogenetic proteins (BMPs), the BMP receptors, and signaling pathways. BMPs play a role in craniofacial and periodontal repair and regeneration. The emerging fields of tissue engineering and biomimetic biomaterials have helped enunciation of the rules of architecture for tissue regeneration including alveolar bone and periodontium.

Regulation of the Acute Inflammatory Response

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The acute inflammatory response is tightly regulated in order to minimize tissue damage. When damage occurs, this can be ascribed to oxidants and proteases released by phagocytic cells. Inflammatory damage in rats has been induced by intrapulmonary deposition of IgG immune complexes, causing complement activation and a cascade of cytokines and chemokines. These products are involved in upregulation of vascular adhesion molecules and in chemotactic migration of blood neutrophils. Intrinsic products of the inflammatory system that regulate the inflammatory process include IL-10 and IL-13 as well as secreted leukocyte protease inhibitor (SLPI) and tissue inhibitor of metalloprotease-2 (TIMP-2). IL-10 and IL-13 prevent breakdown of IkB proteins, preventing activation of NFkB. This greatly attenuates gene activation related to generation of cytokines and chemokines. If any one of these three products is blocked in vivo by antibody, the inflammatory response is significantly enhanced, correlating with greater tissue levels of cytokines and chemokines. TIMP-2 does not affect the NFkB pathway and presumably achieves it protective function by directly blocking metalloprotease-2. These findings indicate that acute inflammatory responses are carefully and effectively regulated.

Interrelationships among Periodontal Infection, Diabetic Status and Cardiovascular Disease

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James Beck, PhD
Steven Offenbacher, DMD, PhD
Center for Oral and Systemic Diseases
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University of North Carolina at Chapel Hill
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The emerging discipline of periodontal medicine concerns the interrelationships between periodontal infection and systemic conditions like diabetes mellitus and cardiovascular disease. To investigate these disease interrelationships, we conducted analyses on preliminary data obtained from 3,937 subjects participating in the dental component of the ongoing ARIC (Atherosclerosis Risk in Communities) study. All subjects received a comprehensive oral examination including the measurement of plaque scores, probing pocket depth and clinical attachment levels. Subjects were classified as having periodontitis if 10% or more of sites exhibited probing depths >3mm and if 60% or more of teeth exhibited a plaque score $\geq$ 1. Subjects were also classified regarding diabetic status on the basis of fasting glucose (FG) levels as healthy (FG<110 mg/dL), pre-diabetic (impaired fasting glucose, FG=110-125 mg/dL) or diabetic (FG>126). Cardiovascular outcomes included the incidence of coronary heart disease calculated from baseline to visit 3, carotid intimal-medial wall thickness (IMT) measured using B-mode ultrasound and arterial calcification assessed with acoustic shadowing. Serum samples were collected and analyzed with ELIZA for markers of the acute phase response (C-reactive protein, interleukin-6) and oxidative stress (8-epi-PGF$_{2\alpha}$). Results indicated that periodontitis affected 20% of subjects with diabetes versus 12% of subjects without diabetes. Similarly, periodontitis affected 19% of subjects with IFG versus 12% in noncases. When a logistic regression model was performed and adjustments made for sociodemographic characteristics, body mass and trigliceride levels, we found an odds ratio of 1.5 for the association of periodontitis and IFG. When the percent of subjects with IFG was graphed versus extent of clinical attachment loss, a dose response relationship between periodontitis severity and IFG was observed. Similar analyses revealed that diabetics with periodontitis were more likely to exhibit incident coronary heart disease versus diabetics without periodontitis (10% versus 6%). Whereas periodontitis and diabetic status independently and synergistically affected IMT in subjects, diabetes in the absence of periodontitis appeared to have little effect on arterial calcifications. Additionally although CRP and 8-epi-PGF$_{2\alpha}$ were elevated in subjects with periodontitis regardless of diabetic condition (except controlled diabetes), serum IL-6 was especially elevated among diabetics with periodontitis. These results reiterate the dynamic interrelationships among these conditions and suggest common inflammatory and metabolic events secondary to chronic oral infection.

Diabetes Control and Periodontal Health

George W. Taylor, DMD, DrPH

Substantial evidence supports considering diabetes as a risk factor for poor periodontal health. There is also evidence for periodontal infection adversely affecting glycemic control in diabetes, although this has been less extensively studied. The purpose of this presentation will be to provide an overview of indirect and direct evidence supporting an adverse affect of periodontal infection on glycemic control.

Indirect evidence comes from investigations of relationships between insulin resistance and active inflammatory connective tissue diseases, other clinical diseases, and acute infection. Due to the high vascularity of the inflamed periodontium, this inflamed tissue may serve as an endocrine-like source for TNFα and other inflammatory mediators. Because of the predominance of Gram negative anaerobic bacteria in periodontal infection, the ulcerated pocket epithelium could constitute a chronic source of systemic challenge for bacterial products and locally produced inflammatory mediators. TNFα, IL6, and IL1, all mediators important in periodontal inflammation, have been shown to have important effects on glucose and lipid metabolism, particularly following an acute infectious challenge or trauma. TNFα has been shown to interfere with lipid metabolism and to be an insulin antagonist. IL6 and IL1 have also been shown to antagonize insulin action. To date, all reports on an infection-related alteration of the endocrinologic-metabolic status of the host have been with acute infections. There is a compelling need to evaluate these relationships in the chronic infection context applicable to periodontal infection.

More direct evidence supporting our current knowledge of the effects of periodontal infection on glycemic control in diabetes comes from treatment and observational studies. There is evidence to support periodontal infection/severe periodontitis having an adverse, yet modifiable, effect on glycemic control. However, not all investigations report an improvement in glycemic control after periodontal treatment. There are major variations in the design, conduct, and results of these studies, thus limiting our current ability form firm conclusions. Perhaps most notable is the identification of only 3 published clinical trials; with 1 trial specifically designed for periodontal treatment in patients with type 2 diabetes.

Published reports vary in the criteria used to define cases with diabetes, type of diabetes studied, baseline glycemic control status, diabetes duration, length of follow-up, classification of baseline periodontal status, measures used to assess periodontal status, and procedures used to treat periodontal disease. Additionally, of the 10 clinical studies providing information on the effects of periodontal therapy on glycemic control, 5 did not include control groups and 4 did not appear to be specifically designed to address the relationship between periodontal therapy and glycemic control (though pertinent data were collected that allowed these studies to assess this relationship).

Despite the variation in the literature, there is a distinction in the effect of periodontal treatment on glycemic control related to the mode of therapy. Studies involving mechanical periodontal treatment alone reported improvement in periodontal status only (i.e. no change in glycemic control), while studies including systemic antibiotics accompanying mechanical therapy reported both an improvement in periodontal status as well as an improvement in glycemic control. It has been hypothesized that these differential results due to antibiotic use (especially doxycycline) may involve several mechanisms, including an antimicrobial effect, modulation of host response, and possibly inhibition of the non-enzymatic glycosylation process. Additional evidence for supporting association between severe periodontitis and increased risk for poorer glycemic control comes from two longitudinal observational studies.

While there is both clinical and epidemiological evidence to support the concept, current knowledge remains equivocal in determining whether periodontal infection significantly contributes to poorer glycemic control in either type 1 or type 2 diabetes. Further rigorous, systematic study in diverse populations is warranted to verify that treating periodontal infections can be influential in contributing to glycemic control management and possibly to the reduction of the burden of complications of diabetes mellitus.

Treatment of Periodontitis in Pima Indians

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Periodontal disease a common, chronic gram-negative infection affects diabetic individuals twice as likely compared to non-diabetics. Infection from periodontal origin has been shown to complicate diabetes mellitus control and increase the occurrence of microvascular and macrovascular diabetes complications. Thus, control of periodontal infection and inflammation is becoming increasingly important in management of the diabetes patients. A treatment regime incorporating ultrasonic debridement combined to systemic doxycycline was effective in controlling periodontal infection in Pima Indians suffering from type 2 diabetes. Patients in the doxycycline-treated groups showed at 3 months after treatment complete elimination of *P. gingivalis* from subgingival plaque and significant gain in clinical attachment level. In addition, patients in the doxycycline-treated groups showed a reduction in levels of glycated hemoglobin ranging from 0.52% to 1.0% compared to baseline values at 3 months after periodontal treatment. A similar periodontal treatment regime was tested in Pueblo Native Americans suffering with type 2 diabetes and severe periodontal disease. Paralleling the results of the Pima Indians trial, levels of glycated hemoglobin in diabetic Pueblo Indians were reduced at 3 months after periodontal treatment. Confirming that effective elimination of periodontal infection and reduction of the associated inflammation results in improvement of control of diabetes mellitus measured by levels of glycated hemoglobin. Therefore, Gram-negative infection of periodontal origin constitutes a previously unrecognized, chronic bacterial challenge complicating diabetes mellitus, and hence increasing the likelihood of complications. Treatment of periodontal infection is an extremely important component of the overall management of the patient with diabetes mellitus and its complications.

Advanced Glycation Endproducts and Their Receptors

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The Receptor for Advanced Glycation Endproducts (RAGE) is a central cell surface receptor for Advanced Glycation Endproducts, or AGEs, the products of nonenzymatic glycation and oxidation of proteins/lipids. AGEs are present in diabetic gingival tissue in both humans and rodents to accelerated degrees compared with nondiabetic, age-matched tissue. We recently developed a model of accelerated alveolar bone loss in diabetic mice treated with the human periodontal pathogen, *Porphyromonas gingivalis*. In these mice, increased accumulation of AGEs co-localized with enhanced expression of RAGE in gingival tissue and was associated with increased levels of cytokines, matrix metalloproteinase (MMP) protein and activity. To test the contribution of AGE-RAGE interaction to accelerated alveolar bone loss in this setting, mice were treated with murine soluble RAGE, the extracellular ligand-binding domain of RAGE, or vehicle, murine serum albumin. In mice treated with sRAGE, dose-dependent suppression of alveolar bone loss, AGE accumulation, cytokine and MMP expression/activity was observed. Our findings link AGEs and RAGE to the pathogenesis of accelerated inflammation and tissue destruction characteristic of diabetic periodontitis.

The Role of Serum Lipids and Macrophage Function in Wound Healing

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Macrophage phenotype may be the determinant of whether connective tissues maintain homeostatic balance, become susceptible to chronic inflammatory destruction, or enter into a state of excessive repair. The normal wound healing response begins with an initial inflammatory phase that proceeds to a granulation phase under the direction of certain biological signaling molecules (pro-inflammatory cytokines and polypeptide growth factors) operating in defined amounts within a specific temporal cascade. This transition from an inflammatory environment to a reparative/proliferative environment is absolutely essential for healing to occur. The initial wound environment (days 1-3 post wounding) is characterized by the presence of large numbers of polymorphonuclear leukocytes (PMNs) and blood monocytes, however, by three days post-wounding, significant numbers of tissue macrophages are present. The tissue macrophage soon becomes the dominant cell in the early wound environment releasing the largest amounts of cytokines and growth factors. Recent literature indicates that all macrophages are not alike. In fact, at least three different macrophage subsets were specifically identified using surface marker antigens. These subsets were differentially observed in clinical conditions associated with chronic inflammatory tissue destruction and tissue fibrosis.

Our previous studies have demonstrated that these different macrophage subsets can be characterized functionally using cytokine profiles. We have identified an inflammatory macrophage phenotype (27E10) that preferentially produces pro-inflammatory cytokines and a reparative/proliferative phenotype (RM3/1) that preferentially produces polypeptide growth factors. We have quantitated the relative amounts of these macrophage subsets in different clinical conditions in both animal and human models. The 27E10 subset predominates in diabetes, hyperlipidemia, chronic non-healing dermal wounds, and periodontitis. The RM3/1 subset predominates in drug-induced connective tissue overgrowth. In vitro studies using animal and human macrophages have confirmed that exposure to serum lipids favors development of the 27E10 subset while exposure to hyperplastigenic drugs favors development of the RM3/1 subset. We have also observed a significant growth factor deficit in diabetic non-healing wounds and in gingival tissues affected by periodontitis. In contrast, we have observed a significant growth factor excess in drug-induced hyperplastic connective tissues. Additionally, we have demonstrated that the diabetic condition, administration of a high-fat diet, and exposure to high levels of serum lipids cause a generalized inhibition of macrophage cytokine/growth factor production. Use of a lipid-lowering drug (fenofibrate) in an animal model favors the RM3/1 phenotype and potentiates macrophage cytokine/growth factor production.

Our investigations indicate that the shift in macrophage phenotype observed in diabetes is caused by elevations in serum lipids (low density lipoprotein cholesterol and triglycerides) and not by hyperglycemia. This is significant as it indicates a need to

consider control of diabetes not only in terms of serum glucose levels but also in terms of serum lipid levels. Additionally, conditions characterized by hyperlipidemia appear to be at risk for development of similar complications. This is of particular relevance in light of our most recent data indicating that periodontitis itself elevates serum lipid levels. This may provide a critical linkage between periodontal disease and systemic conditions such as diabetes and cardiovascular disease.

Matrix Metalloproteinases in Diabetes

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The matrix metalloproteinases (MMPs) responsible for the degradation of the structural extracellular matrix (ECM) components such as the interstitial and basement membrane collagens, fibronectin and laminin play a role in both physiologic and pathologic events. It has been shown that an imbalance between activated MMPs and their host-derived endogenous inhibitors leads to pathologic breakdown of the ECM during periodontitis and numerous other pathologic processes. Furthermore, elevated MMP-levels have been associated with a number of long-term complications of diabetes, including periodontitis. The mechanisms for increased enzyme activity are currently being studied in diabetic rat models. Elevated levels of iNOS, PGE_2, and certain cytokines have all been observed in diabetics, with any or all of these cell regulators being responsible for elevated MMP expression. In addition, advanced glycation end-products (AGEs) formed during long-term diabetes can interact with membrane-bound receptors on inflammatory and resident tissue cells to stimulate their production of a variety of cytokines. In particular, cytokines such as IL-1 and TNF can stimulate the synthesis of MMPs and other matrix degrading enzymes by various cell types. AGEs also have a propensity to form reactive oxygen intermediates which are believed to activate at least some types of pro-MMPs, e.g. pro-MMP-8 which is more susceptible to ROS-activation than other MMPs. Recognition of the need to restore the natural balance between tissue destructive enzymes and their inhibitors led to the development of a disease management strategy which focuses on the adjunctive modulation of MMPs, involved in the terminal catabolic component of the host response in diabetics, in conjunction with conventional measures for glycemic control.

Bacterial Infection in Diabetics

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It is generally accepted that patients with diabetes are more susceptible to the development of infections than those without diabetes. It also is believed that infections in diabetic patients are more severe than the same infection in a non-diabetic individual. However, conclusive studies supporting these clinical impressions do not currently exist (J. Periodontol. 1999; 67:166-176). There is a trend, however, for certain bacterial infections to be increased in diabetes. Included are oral flora in periodontitis, tuberculosis, *H. pylori* (gastric),, group B *Streptococcus*, *Staphylococcus aureus* (pulmonary), *Klebsiella* (urinary tract), and *Salmonella* (enteritis). For periodontitis, the microorganisms that are risk indicators include *Porphyromonas gingivalis, Prevotella intermedia, Actinobacillus actinomycetemcomitans, Eikenella corrodens, Fusobacterium nucleatum, Bacterioides forsythus, Campylobacter rectus,* and *Spirochetes* or *Treponema* species. *In vitro* studies of host defenses show that diabetics may have impaired defense mechanisms which involve the macrovascular circulation, the microvascular circulation, wound healing, collagen metabolism, inflammatory tissue damage (proteolysis, acidity, oxidation), neutrophils (chemotaxis, phagocytosis, and adhesion), response to dental plaque, and glycation of proteins and lipids. Also the literature indicates that bacterial infections are exacerbated in the presence of diabetic complications such as vascular disease and metabolic dysfunction. The impaired defense mechanisms in diabetes will be discussed from the perspective of normal host defenses. For prevention and therapy of bacterial infections in diabetics, tight control of diabetes and removal of calculus is important.

Microbial Considerations in Periodontitis

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One of the complications of diabetes in some patients appears to be a more aggressive form of periodontal disease. Periodontal diseases are infections caused by the organisms that colonize the tooth surface at or below the gingival margin. The organisms in this habitat exist as biofilms; i.e. complex mixtures of microorganisms protected by a glycocalyx. The biofilm provides a protected environment that makes bacterial control difficult either by the host or the therapist. Recent studies using checkerboard DNA-DNA hybridization have revealed associations among species and communities of organisms in dental biofilms and have related the resulting "microbial complexes" to factors affecting local or systemic habitat such as health or disease, pocket depth, local inflammation, smoking and therapy. One of the more important microbial communities appears to be the "red complex" consisting of *Porphyromonas gingivalis, Bacteroides forsythus* and *Treponema denticola*. Species of this complex are found in higher prevalence, proportions and counts in subjects with periodontitis compared with periodontally healthy individuals. These species are elevated in deep periodontal pockets, in gingivitis and in subjects who are current smokers. "Red complex" species appear to colonize adjacent to the epithelium lining of the periodontal pocket. Further, studies have shown that *P. gingivalis* and *B. forsythus* can invade epithelial cells. Successful periodontal therapy is often associated with a reduction in levels of the "red complex" species. A second "orange complex" consisting of *Fusobacterium, Prevotella* and *Campylobacter* species is often associated with and may precede colonization by the "red complex". Other complexes and species, particularly members of the genus *Actinomyces* appear to be associated with periodontal stability. These species together with members of the genera *Streptococcus, Veillonella* and *Capnocytophaga* are the initial colonizers of dental biofilms and provide the framework for its organization. A number of studies have examined the subgingival microbiota in diabetic subjects. However, these studies were inconclusive in defining microbial changes brought about by the diabetic state. New, rapid microbial identification techniques should allow a more comprehensive evaluation of subgingival biofilms associated with diabetes and describe differences that might occur between the diabetic and systemically healthy subject.

Periapical Lesions in Non-Obese Diabetic Mice

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Uncontrolled or poorly controlled diabetes mellitus (DM) may be a risk factor for the development of large and/or debilitating periapical infections. The purpose of this investigation was to use the non-obese diabetic (NOD) mouse to determine the effect of DM on several factors associated with the progression of periapical lesions. Factors studied included morbidity (weight loss) and mortality of the animals, periapical lesion size and its expression of selected bone-modulating cytokines. DM was detected in 34 of 46 (74%) of female NOD/MrkTac mice (Taconic) by age 17-30 weeks, as determined by glucosuria and insulitis seen in post-euthanasia pancreatic biopsies. Periapical lesions were induced in 27 female diabetic NOD mice in mandibular first molars. The animals were divided into two groups: Group A had 5-week (chronic) pulp exposures and inoculations with 100 µl of 3x10(8) cells/ml each of a mixture of *Fusobacterium nucleatum*, *Peptostreptococcus micros* and *Streptococcus intermedius*, or exposures without inoculations. Group B had acute exposures that were inoculated and sealed by a composite bonding agent for 1 week or were exposed for 2 weeks with neither inoculation nor the seal. In the chronic inoculation group, cavities were re-inoculated at biweekly intervals. Equivalent numbers of female BALB/c mice were used as controls. Animals that survived to the end of the pre-designated periods were sacrificed, the mandibular halves were processed for histomorphometric measurement of lesion size, and for quantitative immunohistochemical staining for IL-1a, IL-6 and IL-4.

In Group A, 38% of the inoculated and 38% of the uninoculated NOD mice died before the end of the 5-week period, some with severe facial infections. None of the BALB/c mice died during the 5-week period. In Group B, 83% of the NOD mice that had inoculated and sealed exposures died within 1-4 days, whereas only 29% of the equivalent BALB/c mice died within 4-5 days. None of animals of both strains that were exposed for 2 weeks but neither inoculated nor sealed died. The surviving NOD mice lost significantly more weight at the time of sacrifice than BALB/c mice. Periapical lesion size and cytokine expression in the surviving animals of both strains were not significantly different. DM caused the development of clinically more significant periapical infections. For diabetic mice that did not develop severe infections, the size of periapical lesions and their cytokine content was similar to controls. (Supported by a USPHS grant #1R55-DE/OD12037-01A1.)

INFECTION AND INSULIN RESISTANCE.

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Historically, one of the most common characteristics of patients after traumatic injury or infection is the presence of impaired glucose tolerance. This decreased rate of glucose clearance following a glucose tolerance test implied, but did prove, the existence of an insulin resistant condition. Recent studies in humans and animals, using the euglycemic-hyperinsulinemic clamp technique, clearly demonstrate that infection impairs the ability of insulin to stimulate glucose uptake by the whole body. In contrast, the ability of insulin to suppress hepatic glucose output appears to be largely unaltered by sepsis. In additional studies, in which we have combined the hyperinsulinemic clamp with the injection of ^{14}C-2-deoxy-glucose, the sepsis-induced defect in whole body insulin action can be localized primarily to skeletal muscle. Insulin-mediated glucose uptake (IMGU) by other tissues, such as fat, heart and skin, does not appear to be significantly altered by sepsis. In skeletal muscle, under hyperinsulinemic conditions, the amount of glucose directed toward glycolysis and oxidation is not altered by sepsis. However, there is a greater than 50% reduction in the amount of glucose uptake shunted toward glycogen. Relatively little work has been done on the intracellular mechanisms responsible for this defect. It is known, however, that while the number of insulin receptors appears unaltered by sepsis, the ability of insulin to stimulate various components of the insulin signal transduction pathway is decreased. Specifically, the extent of phosphorylation of the insulin receptor, IRS-1 and MAP kinase in response to insulin is greatly impaired in muscle from septic rats. In vivo studies have demonstrated that infusion of the nonspecific B- adrenergic antagonist propranolol, but not the B_1- antagonist atenolol, can largely prevent the development of the sepsis-induced peripheral insulin resistance.

ln contrast, we could find no evidence that overproduction of the inflammatory cytokine TNF was responsible for the impairment of IMGU in septic rats, although the infusion of recombinant TNFa into control rats is capable of inducing an insulin resistance condition. In summary, it is clear that sepsis impairs IMGU by the whole body, and this impairment is primarily localized to a defect in nonoxidative glucose disposal in skeletal muscle. Numerous defects in the insulin signaling pathway are associated with the decrease in IMGU. Finally, our data suggest that adrenergic stimulation, probably mediated by a $\sim_2$madrenergic mechanism, plays a prominent role in the development of the insulin resistance in septic rats. (Supported by NIH GM 38032).

Hormonal Regulation Of Salivary Glands In Diabetes

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Saliva plays an important role in the protection of the oral cavity, and alterations in either salivary flow rate or protein composition may have dramatic effects on oral health. There is, however, a considerable divergence of opinion in the published literature as to the extent, or even existence, of changes in salivary gland function in insulin-treated, human diabetic patients. Nonetheless, over the past forty years it has become clear that insulin and "insulin insufficiency" have both direct and indirect effects on the structure and function of rodent salivary glands. The observed effects are dependent on the duration of the disease, the gland and the cell type under study. For example, insulin appears to play a direct role in the regulation of gene expression in parotid acinar cells, whereas its role in modulating mRNA transcription and protein synthesis in the granular ducts of the submandibular gland is largely indirect, mediated via the effects of diabetes on pituitary-dependent hormones. Further, we know that the effects of diabetes on protein synthesis/secretion and fluid formation may be independent of one another. Because the initiation of salivary secretion requires neural stimulation, it is also important to consider how diabetes affects either cellular responsiveness to neurotransmitters and peptides, sympathetic and parasympathetic nerve function, or both. Finally, the role of the vasculature in salivary secretion is often ignored, but salivary gland fluid production involves the movement of water out of the capillaries into the interstitial tissue, and thence across the glandular epithelium into the lumen. Abnormalities in vascular physiology, therefore, might be expected to have a profound impact on salivary gland function in diabetes.

Salivary Gland Dysfunction In Autoimmune NOD Mice

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Sjögren=s syndrome is a human disease characterized by exocrine dysfunction presumed to result from the destruction of salivary and lacrimal glands by a progressive autoimmune attack. Although Sjögren=s syndrome can occur as a primary autoimmune disease, it is more likely to present clinically in connection with other autoimmune diseases, e.g., SLE, Rheumatoid Arthritis or IDDM. Women are 9 times more likely than men to be afflicted. In order to elucidate the underlying mechanisms of Sjögren=s syndrome, we turned to the NOD mouse as an animal model for autoimmune exocrinopathy. NOD mice, while genetically predisposed to develop autoimmune diabetes, exhibit leukocytic infiltrates of the salivary and lacrimal glands, circulating autoantibodies to acinar cell-associated proteins, biochemical changes in secretory proteins, and marked reductions in exocrine gland flow rates. In addition, the use of a variety of congenic partner strains of NOD, e.g., NOD-$scid$, NOD.B10.$H\text{-}2^b$ and NOD.Igì^{null}, has provided insight into the relationship between IDD and autoimmune exocrinopathy in this model, as well as possible roles for genetically pre-determined temporal physiological alterations versus the immune response in development of exocrine gland dysfunction. Physiological changes that occur in the absence of and prior to detectable autoimmunity include: delayed salivary gland organogenesis, aberrant expression of specific secretory proteins, activation of proteolytic enzymes (especially MMPs), increased acinar cell apoptosis and biochemical changes of secretory proteins. Characteristics of the autoimmune response include: requirement for B lymphocytes, restriction of leukocytic infiltrates primarily to lacrimal and submandibular glands (i.e., absent from parotid glands), rise in proinflammatory cytokines detectable in salivary glands, and a primary role for IgG autoantibodies to achieve loss of salivary flow. These observations suggest that salivary gland dysfunction is manifested by physiological factors, but mediated by humoral immunity - a concept supported by recent experiments in which NOD.Igì^{null} mice infused with serum IgG from Sjögren=s syndrome patients or NOD mice with overt exocrinopathy exhibited rapid loss of secretory function. With sera from Sjögren=s syndrome patients and NOD mice containing autoantibodies reactive to numerous exocrine cell-associated molecules, including SS-A/Ro, SS-B/La, á-fodrin, PSP, nuclear antigens, â-adrenergic and muscarinic cholinergic receptors, the question arises AWhat is the autoantigen(s) responsible for this activity?@ Based on the fact that the principal factors regulating saliva and tears are the autonomic neurotransmitters released by innervating nerves, plus preliminary data suggesting a primary role for the muscarinic cholinergic receptor (M_3), we set about to determine if anti-M_3 antibodies can effect salivary gland dysfunction. An expression vector, containing a PCR-generated sequence for the open-reading-frame of the rat M_3 receptor, was used to transfect COS-7 cells. M_3 receptor-expressing COS-7 cells were selected by G418 resistance and cloned. M_3 was purified from the membranes of COS-7 and used to immunize NOD.B10.$H\text{-}2^b$ mice. Sera from the immunized mice were tested using Western blots until strong anti-M_3 reactivity was obtained. After 6 immunizations, spleens were removed from the

NOD.B10.$H\text{-}2^b$ mice and fused with the SP/0_2 myeloma to produce hybridomas. Following cloning, 4 hybridomas reactive with M_3-transfected, but not untransfected, COS-7 cells were selected. To examine the effects of these anti-M_3 antibodies, each polyclonal and monoclonal antibody was infused into NOD.Igì^{null} and/or C57BL/6-*scid* mice. Within 24 hrs, mice infused with anti-M_3 receptor antibody exhibited loss of secretory function. Infusions of anti PSP or anti-SS-B/La had no effect on secretory capacity. These results confirm that antibodies reactive to the extra-cellular domains of the M_3 receptor precipitates salivary gland dysfunction. The presence of the M_3 receptor on intestinal smooth muscle, vascular smooth muscle, iris sphincter muscle, as well as exocrine pulmonary, vaginal and dermal sweat glands, may explain the involvement of these organs in Sjögren=s syndrome.

Regulation of Autoimunity ID the NOD Mouse:
The Natural History of the CD4+CD+ Lymphocyte

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The Non Obese Diabetic (NOD) mouse is used as a model to study type I diabetes and Sjogren's syndrome. Results from research with the NOD mouse as well as other mouse models of autoimmune disease have shaped how we think about autoimmune disease, and have provided a significant framework for directing and focusing research in individuals with autoimmune disease. In this project, we are working with a cell type, the CD4+ lymphocyte that has been traditionally thought necessary to cause disease. Recent evidence has suggested that a sub-population on of CD4+ cells (i.e., CD4+CD25+ T lymphocytes) can actually prevent the initiation and possibly the progression of autoimmune disease.

In a normal non-autoimmune mouse model (BALB/c), it has been shown that the removal of the CD4+CD25+ population results in autoimmunity. This suppressive population has been shown to be anergic, to need cell-cell contact to exert its suppressive activity, and to not use a soluble factor (i.e., cytokine) for suppressive activity (1). In the NOD mouse, it has been shown that neonatal administration of anti-TNF will completely prevent insulitis and the onset of diabetes (2). The effect of neonatal anti-TNF in the salivary gland is not as well documented, but the diffuse lymphocytic infiltrate still develops (3).

In this study, we have measured the percentage of CD4+CD25+ T cells in the thymus, pancreatic lymph node, salivary gland lymph node, inguinal lymph node, and spleen a 3,8, 15 and 30 weeks in both NOD and BALB/c mice. In addition, we have examined tile effect of neonatal administration of anti-TNF on the percentage of CD4+C25+ lymphocytes in the aforementioned lymphoid organs at 4 weeks in NOD and BALB/c mice. The results show striking differences in the percentage of CD4+CD25+ lymphocytes in NOD thymus, pancreatic lymph node, salivary gland lymph node, inguinal lymph node, and spleen when compared to the BALB/c mouse. The results also indicate that neonatal administration of anti-TNF can regulate this cell population in the NOD mouse

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Dental Utilization and Cost Among Diabetics in an HMO.

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The impact of diabetes mellitus on oral health has been well documented; however, no studies have reported on the use and cost of dental services among diabetics. The purpose of this study is to describe dental care use and cost in a large HMO. By linking the HMO's diabetes registry with other medical and dental databases, a study population was identified of confirmed, nongestitational diabetics with continuous medical and dental eligibility between 1/1/93 and 6/30/96 (n=3,537). For each diabetic study subject, we randomly selected a nondiabetic member matched on eligibility, age (mean age of 58 years as of 6/30/96), and gender (49.3% female). An association was found between diabetic status and the number of subjects with a dental visit (X^2=13.91, df=1, $p \leq 0.0002$). About 83.5% of diabetic study subjects and 87.1% of nondiabetic study subjects had at least one dental visit during the study period. No difference in the mean number of visits was found between the two groups (10.2 for diabetics versus 9.9 for nondiabetics). About 19.3% of diabetics and 15.1% of nondiabetics had at least one extraction during the study period. Age group and diabetic status were associated with whether a person had an extraction during the study period (X^2=19.2, df=6, $p \leq 0.004$). Differences in the proportion of diabetics and nondiabetics with at least one extraction were greatest in the 31-40 age group; 23.3% of diabetics had at least one extraction compared with 9.9% of nondiabetics. The mean number of extractions differed significantly for the two groups (0.6 for nondiabetics and 0.8 for diabetics; p=0.0001). The mean cost of dental care for diabetics was $1,195.67 (1996 dollars) and for nondiabetics was $1,263.22 (unequal variance; t=2.219, df=7,056, p=0.027). In an HMO, diabetics tended to use dental services less frequently than nondiabetics. More diabetics had extractions than nondiabetics, and the mean number of extractions differed. Extractions in diabetics tended to occur earlier. Overall cost of dental care among diabetics was lower than among nondiabetics. Supported by NIDCR Grant DE12034.

Oral Health and Glycemic Control in the Elderly

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Four out of every 10 adults over the age of 65 years in the USA have diabetes mellitus or impaired glucose tolerance. There is a significant age-related increase in prevalence rates of diabetes and impaired glucose tolerance, and the prevalence of these disorders has increased 30-40% in the elderly over the past 20 years. The oral complications of diabetes have received considerable epidemiological, clinical, and basic science research investigation, particularly in the areas of gingival and periodontal diseases. However, few efforts have been dedicated towards understanding the oral complications of diabetes in the older population.

This presentation will summarize some of the connections between diabetes and oral health in older adults. Gingival and periodontal diseases have received the most amount of research attention. There appears to be greater amounts of gingivitis and periodontitis in adult diabetics, and poor glycemic control has been associated with worse periodontitis. Importantly, there is data to suggest that periodontal infections have an adverse effect on glycemic control. The connection between dental caries and glycemic control in older adults is less clear. The majority of reports demonstrate a potential link between greater caries rates in poorly-controlled diabetics, which may result in greater tooth loss. Many older diabetics complain of thirst and xerostomia, which has created considerable research attention dedicated towards understanding the relationship between diabetes and salivary physiology. However, a clear connection between salivary disorders and diabetes has not been established. There are some data to suggest that there may be impaired salivary flow rates and constituents in poorly-controlled diabetics. Oral mucosal lesions, particularly lichen planus, have been reported in diabetics. Impaired gustatory and olfactory function has been attributed to diabetes that could result in nutritional deficiencies or dietary complications. Finally, there is some data linking peripheral neuropathies, such as burning mouth syndrome, with diabetes.

The elderly are the most rapidly growing portion of the population in the USA, and diabetics are living longer due to improved diagnosis and management. Furthermore, adults are retaining their teeth longer than previous cohorts. Therefore, it can be anticipated that in the future there will be a substantial number of older dentate adults with diabetes, susceptible to the oral complications of controlled and uncontrolled diabetes. Greater research is needed to identify risk factors for oral and craniofacial diseases in older diabetics, and to develop management and prevention strategies to preserve and enhance the oral health of older diabetics.

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The NIDCR supported $2.2 million (21 projects) in diabetes research in fiscal year 1998, the most recent year for which we have data. Of this amount, $1.4 million (19 projects) was from the Division of Extramural Research and $0.8 million (2 projects) was from the Division of Intramural Research. Seven projects supported by the NIDCR were contained in Center grants that have ended or will be coming to a close soon. Only eight projects [one Center subproject, one R01 grant, two R29 (FIRST awards), two R03 (small grants), one Intramural Project, and one Interagency Agreement] were devoted completely to research on Diabetes.   With regard to science, five projects focused on pathogenesis of oral complications, five on the natural history/association of oral complications and diabetes, four on associations of diabetes with oral diseases severity, two on oral health evaluation in diabetics, and one project each on pain, treatment of periodontitis in diabetics, and training of clinicians to understand the link between periodontitis and diabetes.   The last major diabetes initiative by the NIDCR, an RFA issued in 1994 titled Research on Periodontal Complications of Diabetes, resulted in submission of 17 applications. Only one application received a score below 200 and was funded.   Unsuccessful applicants were encouraged to revise and resubmit, and of the five who did, one was funded.

The NIDCR is working in collaboration with other NIH Institutes, Federal agencies and professional organizations to identify and support premier research in the area of diabetes and oral health.   Currently funded projects are leading the field in helping us understand the links between diabetes and oral diseases. Clearly there is a need for revitalization and expansion of work on this topic. The results from today's workshop will help to identify the key areas of research that could benefit from additional support.

RECOMMENDATIONS FOR FUTURE RESEARCH

Throughout the meeting, participants were asked to provide recommendations for future research based on their own experience, what colleagues had told them, and the information they learned at the workshop. Listed below are the recommendations that were received for the major scientific topics covered during the workshop.

I. General

The complications associated with diabetes must be studied in patients with various forms of diabetes.

Recommendations:

1. Include studies on the oral complications of both Type 1 and Type 2 diabetes.

2. Encourage the development and use of novel animal models (genetically characterized mice, SCID mice, gene knockout mice), particularly genetic models of Type 2 diabetes, to dissect the mechanisms of pathogenesis and to study the oral complications of diabetes.

II. Infectious Diseases

Oral infections, particularly periodontal diseases, are major complications of diabetes. Therefore, a large part of the meeting was devoted to this topic.

Recommendations:

1. Evaluate the natural history of oral infections in diabetes from a microbial perspective.

2. Examine the differences in microflora using checkerboard hybridization analyses in diabetic patients to compare it to that found in healthy controls.

3. Examine the microbial flora for virulent sub-clones using molecular/DNA hybridization techniques.

4. Determine the susceptibility of the diabetic patient to oral infections.

5. Study microbe-host cell interactions at the molecular level.

6. Study the etiology and pathogenesis of pulpal and periapical infections in diabetic patients.

7. Conduct long-term longitudinal studies to evaluate the microbial flora over time in controls and diabetic patients.

8. Determine what effect diabetes treatments have on the oral microflora.

9. Continue to study microbial pathogenesis in animal models of diabetes, recognizing that better animal models may be needed. Take into consideration the normal oral flora of each model system.

10. Determine the possible entry of hepatitis C via oral tissues.

11. Re-evaluate the occurrence and severity of caries in poorly controlled diabetic patients.

III. Inflammation and Immunity

Inflammation and immune responses are negatively influenced by diabetes. Clearly, the host response to exposure to foreign microbes and to the healing process needs further clarification.

Recommendations:

1. Evaluate the entire mucosal immune capacity of the diabetic patient, including salivary gland function; synthesis, structure and secretion of sIgA; number and type of lymphocytes; and innate immune response.

2. Characterize host responses, including cytokines and lymphokines, specific for oral microbes and microbial biofilms in the diabetic patient, and compare these to those found in healthy controls.

3. Compare and contrast the immune responses to oral pathogens in diabetics and normal controls.

4. Determine how the immune responses are related to glycemic control.

5. Study the connection between serum lipids and immune cell function.

6. Examine the nature of the microflora and host mediators in healthy individuals and diabetic subjects who do or do not have periodontitis.

7. Use sensitive and specific techniques that permit evaluation of large numbers of host and microbiological markers in large number of subjects.

IV. Bone & Connective Tissue

A devastating complication of diabetes is the loss of bone and connective tissue associated with the oral cavity.   This seems to be an advanced area of research that could benefit greatly from additional research.

Recommendations:

1. Study the correlation of oral and systemic bone loss in the diabetic patient. Use these data to study the mechanisms of pathogenesis and to develop new therapies.

2. Study the pathogenesis of bone formation / breakdown in diabetic animals. What role do bone morphogenetic proteins play in this process?

V. Vascular Disease

The periodontium contains highly vascularized tissues. Since diabetes has profound effects on the microvasculature, the effects of diabetes on the gingival tissues could be great. The oral cavity provides an unparalleled opportunity to examine and follow the pathogenesis of vascular diseases in situ.

Recommendations:

1. Study the source and characteristics of growth factors involved in vascular diseases in the diabetic.

2. Determine whether oral tissues are a good site to detect and measure vascular hyper-permeability.

3. Examine what effect vascular hyper-permeability has on salivary glands and salivary gland function.

VI. Neuropathy

Another oral complication of diabetes is alterations in taste sensation and burning mouth.

Recommendations:

1. Additional studies are needed to evaluate and characterize taste and smell alterations in diabetic patients.

2. Study oral pain in the diabetic animal/patient.

3. Determine whether pulpal pain be used as a model.

4. Explore what effects diabetes has on oral nerves, neuronal healing, and production of growth factors by neural cells.

VII. Genetics

Both diabetes and periodontitis appear to be genetically complex diseases. Nonetheless, recent studies and new techniques are providing insight to the involvement of genes in both of these diseases.

Recommendations:

1. Elucidate the genetic relationships between diabetes and periodontitis.

2. Characterize individual genetic differences, using single nucleotide polymorphisms and high density maps, to better understand the genetic basis for the oral complications of diabetes.

3. Clinically assess the oral health of subjects in ongoing or forthcoming diabetes genetic studies. This will provide a cost-effective approach to increase research on the genetics of oral diseases.

4. Study the genetics of inflammatory mediators.

5. Increase research on genetic epidemiology of periodontitis, diabetes and diabetic complications.

VIII. Saliva and Salivary Glands

Changes in salivary composition and salivary dysfunction are frequent complications of diabetes. Because the role of saliva is so critical to oral health, more research is needed on this topic.

Recommendations:

1. Using specific patient populations, such as poorly controlled diabetics, further characterize the changes in salivary tissue (both major and minor salivary glands) in diabetes. Are these changes similar to those found in other tissues?

2. Determine the effects of changes in saliva (both gland specific and whole saliva) composition on oral microbial biofilms.

3. Determine whether saliva can be used as a noninvasive marker of diabetes and glycemic control.

4. Explore the possible use of genetically altered oral keratinocytes as a source of insulin production in animals.

5. Use a modified NOD mouse model having only one defect.

6. Investigate the relationship between salivary flow and composition with the capacity of the diabetic patient to self-report dry mouth (xerostomia).

7. Use genetic microarray technology to identify novel and important genes turned on/off in the oral tissues of diabetic animals.

8. What are the pathogenic mechanisms of autoimmunity in salivary glands in diabetics.

IX. Behavior

A separate workshop was held on this topic recently [{insert name and URL here}]. The current workshop similarly considered behavior to be an integral part of both the cause and solution to oral complications of diabetes.

Recommendations:

1. Encourage research on behavior modification in order to get the patients to come to dental office, improve their diet, access oral health care givers, and be compliant with treatment protocols.   Develop new techniques to assess behavior modification.

2. Determine whether tight blood glucose control reduces the oral complications of diabetes?

3. Encourage oral researchers to attend and present their data at diabetes-related meetings .

4. Encourage oral researchers to publish data and review papers in diabetes journals.

X. Systemic Diseases:

As the workshop progressed, it became clear that diabetic complications in the oral cavity could be related to those found in various other body locations. The relationship between disease in one part of the body appears to be intricately tied to disease in other parts of the body. Thus, treatment of one complication might have a beneficial influence on other complications.   Similarly, as a logical, yet unproven, extension of the DCCT results,

metabolic control of diabetes could have beneficial effects on all complications, including those in the oral cavity.

Recommendations:

1. Explore connections between periodontitis and other diabetic complications (e.g., retinopathy, nephropathy).

2. Encourage researchers to evaluate the effects of periodontal therapy on diabetes as well as complications of diabetes, including cardiovascular diseases, retinopathy, nephropathy.

3. Show that strict control of blood glucose can reduce oral complications of diabetes (e.g., periodontitis, salivary function, and taste/smell). Determine the effect of early intervention on the development and rate of progression of oral complications of diabetes.

4. Show that treatment of oral complications reduces the severity or incidence of other complications of diabetes

5. Show that treatment of diabetes with contemporary approaches has a positive effect on oral health.

6. Determine whether periodontitis increases the risk for development of Type 2 diabetes (or other systemic diseases, for example, cardiovascular diseases) in all or some subpopulations of individuals.

XI. Clinical studies:

The need for new and well designed clinical studies to evaluate the associations between oral complications and diabetes was articulated by many of the participants as the number one priority issue.

Recommendations:

1. Determine the effects of host immunomodulatory therapy on diabetic complications.

2. Examine and assess appropriate treatment therapies for periodontal diseases in the diabetic patient. Determine how clinical periodontal therapy can be designed to specifically help diabetic patients.

3. Increase research on oral complications of diabetes in the elderly. Evaluate the effects of aging on the oral complications of diabetes. The rapidly growing

subpopulation of frail elderly and "old-old" represents an excellent opportunity for expand studies on diabetes and oral health.

4. Determine the appropriate therapeutic endpoints to be measured for {what ?????
    Need some help here}.

5. Show that treatment of oral infections can have a beneficial role on the oral microbial flora, diabetes (e.g., glycemic control), and other diabetic complications (e.g., retinopathy, nephropathy.)

6. Determine whether lipid-lowering therapies have a beneficial effect on the complications associated with diabetes, periodontitis, and other chronic inflammatory diseases.

XII. Translation Research:

1. Apply information learned from animal models to develop therapies that can be used in randomized clinical trials in human.

2. Translation and disseminate information about the bi-directional relationship between diabetes and periodontal disease into the knowledge-base and clinical practices of non-dental health care providers.

3. Study the feasibility of using diagnostic approaches for diabetes mellitus in the dental office utilizing laboratory analysis of blood, urine, saliva and gingival fluid. Determine if there are specific tests that can identify patients with diabetes who are at risk of developing periodontal disease.

XIII. Administration

Establish a NIDCR "Scout Group" to search for opportunities to include oral sub-studies in large diabetes and obesity studies.

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