Diabetology

RSSDI

Yearbook of Diabetes 2017

Editor-in-Chief
Sujoy Ghosh

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Yearbook of
Diabetes
2017

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Message from the RSSDI President

The RSSDI Yearbook of Diabetes 2017 brings you the abstracts of the articles that reported 2 years recent and breakthrough developments in diabetes, carefully selected from many journals worldwide. Expert commentaries evaluate the clinical importance of each article.

This allows the reader to quickly identify and understand topics of interest which translates into practical application. The goals of the book are to be current, to be compact, to make the information accessible, and to be understandable by students of medicine of all ages.

The book is divided into 12 sections arranging closely related subjects into clusters. The sections span the spectrum of diabetes from basic science to future directions.

Together we salute and thank the Editor-in-Chief Dr Sujoy Ghosh for his expertise in the shaping and collation and for showing extraordinary commitment to maintaining the excellent standard. We are especially grateful to the editorial team comprising Dr Soumik Goswami, Dr Amritava Ghosh, Dr Sanjay Kalra, Dr Indira Maisnam, Dr Anuj Maheshwari, Dr Rana Bhattacharjee, Dr Sayantan Ray, Dr Rakesh Sahay, Dr Ajitesh Roy, Dr Rajeev Chawla, Dr Partha P Chakraborty, Dr Sanjay Agarwal, Dr Anirban Sinha, Dr Deep Dutta, Dr Kaushik Pandit, Dr Pradip Mukhopadhyay, and Dr Chitra Selvan who have provided endless support. We would also like to thank the editorial assistants Dr Anjan Roy, Mr Kingshuk Bhattacharjee, and Dr Ranjini Sen who have been instrumental in compiling this extensive work.

We all take immense pride in producing an outstanding book and hope that the reader will agree that the excellence of the writing and scholarly rigor displayed by the authors make a strong argument for its endurance as an outstanding resource for education and teaching in diabetes.

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Message from the RSSDI Secretary

It is indeed a matter of great pride that Research Society for the Study of Diabetes in India (RSSDI) is publishing "RSSDI Yearbook of Diabetes 2017" which will be released at the 45th RSSDI Annual Conference of the RSSDI at Bhubaneshwar on 3–5 November 2017. One of the key endeavors of RSSDI has been to promote research and education in the field of diabetes in India. A "yearbook," a compilation of assorted research papers in diabetes and allied subjects published during the preceding one year will be an important source of all the recent developments in understanding of diabetes and provide a great knowledge tool for physicians, postgraduates, and researchers. Hopefully this will ultimately translate into motivation for more research in diabetes and better patient care. Personally, I am more than pleased to be part of this great educational venture. My compliments to Dr Sujoy Ghosh and the editorial team and my best wishes for the RSSDI Yearbook of Diabetes 2017.

Brij M Makkar MD FRCP FACE
Honorary Secretary, RSSDI
Director
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New Delhi, India

Preface

Incidentally, yearbooks in various specialties are available for almost all specialties and sub-/super-specialties of medical sciences. However, a yearbook of diabetes is not available. Given the fact that 44,337 articles related to diabetes have been published on PubMed in 2016 itself, it is not surprising that no one has embarked upon taking the herculean task of writing a yearbook on diabetes.

Being a teacher, I have been often asked by students which studies to read and how to interpret them. Clinicians, both primary care and specialists often attend conferences and clinical meetings with the expectation to update their understanding of diabetology. Clinical service delivery makes it difficult for most to keep abreast with all the new studies published. Others have at various points expressed their inability to interpret clinical studies and at other times physicians have been swayed by deliberate or inadvertent biased interpretation of clinical studies both by pharmaceutical companies as well as "key opinion leaders."

Hence, it is imperative that a yearbook containing the most important publications are summarized in an easy to read format for the physician be published. The Research Society for the Study of Diabetes in India (RSSDI) is one of the biggest organizations in the field of diabetology worldwide and is, therefore, the apt organization to take up the responsibility.

But why did I agree upon taking this challenge? As I took up this challenge with our editorial team/authors, I was reminded of the words of Authur Conan Doyle (The Hound of the Baskervilles), "the boldest, or it may be the most drunken, rode forward."

We decided to screen all diabetes related (major publications, from major journals) published between 1st July 2016 and 30th June 2017. We screened almost 30,000 original research articles and then divided up the selected articles into 12 subsections and wrote up a critical appraisal of all the selected ones. The unstructured write-ups tried to provide background information on what was already known about the issue prior to the particular publication, what the study added in terms of medical knowledge, and what the take home for the physician is, as well as highlights the possible strengths and limitations of the study and the scope of future research.

I was fortunate to be working with an outstanding team of doctors, including a dynamic editorial team consisting a mix of a biostatistician and doctors (including specialist in pharmacology), physicians, diabetologists, and endocrinologists. I would like to put on record my thanks to my editorial assistance team of Dr Anjan Roy, Mr Kingshuk Bhattacharjee, and Dr Ranjini Sen. The entire writing team of doctors for the book have done a splendid job, that too at such short notice.

I am highly indebted to all the members of the Executive Committee of RSSDI, especially Dr Sarita Bajaj, Dr Brij Mohan Makkar, Dr Rajeev Chawla, and Dr SR Aravind. We also acknowledge the kind support and help that we have received from the American Diabetes Association and

several other international publishing houses and national journals/associations in providing us permission to reproduce abstracts of articles published in their journals.

The entire process of completion of this book has been a roller-coaster journey. Particularly because of the copyright issues and other technical matters. The book would never have seen the light of day without the persistence, help, support, and guidance that I received from Mr Sabyasachi Hazra of Jaypee Brothers Medical Publishers (P) Ltd.

Finally, I would like to thank all my colleagues at work and my family who have been a constant source of encouragement and support.

I dedicate this book to all those involved in the management of patients with diabetes and hope this helps in improvement of patient care and outcome.

Sujoy Ghosh

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1. Long-term Prediction of Cardiovascular Outcomes by Circulating CD34$^+$ and CD34$^+$CD133$^+$ Stem Cells in Patients with Type 2 Diabetes

Ref: Fadini GP, Rigato M, Cappellari R, et al. Long-term prediction of cardiovascular outcomes by circulating CD34$^+$ and CD34$^+$CD133$^+$ stem cells in patients with type 2 diabetes. Diabetes Care. 2017;40(1):125-31.

ABSTRACT

Objective: Cardiovascular risk varies substantially in the population with diabetes, and biomarkers can improve risk stratification. Circulating stem cells predict future cardiovascular events and death, but data for the population with diabetes are scant. In this study, we evaluated the ability of circulating stem cell levels to predict future cardiovascular outcomes and improve risk discrimination in patients with type 2 diabetes.

Research Design and Methods: A cohort of 187 patients with type 2 diabetes was monitored for a median of 6.1 years. The primary outcome was time to a first cardiovascular event, defined as 3-point major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) plus hospitalization for cardiovascular causes. At baseline, we measured six stem/progenitor cell phenotypes in peripheral blood based on expression of CD34, CD133, and KDR.

Results: The primary outcome occurred in 48 patients (4.5/100 patient-years). Patients with incident cardiovascular events had significantly lower CD34$^+$ and CD34$^+$CD133$^+$ cells than those without. Higher rates of cardiovascular events occurred in patients with below median levels of CD34$^+$ and CD34$^+$CD133$^+$. In Cox proportional hazards regression analyses, a reduced CD34$^+$ (hazard ratio 2.21 [95% CI 1.14-4.29]) and CD34$^+$CD133$^+$ [2.98 (1.46-6.08)] cell count independently predicted future events. Addition of the CD34+ cell count to the reference model or the UK Prospective Diabetes Study risk engine improved C statistics, continuous net reclassification improvement, and/or integrated discrimination index.

Conclusions: In patients with type 2 diabetes mellitus, a reduced baseline level of circulating CD34$^+$ stem cells predicts adverse cardiovascular outcomes up to 6 years later and improves risk stratification.

Patients with diabetes and vascular disease have lower levels of circulating CD34$^+$ stem cells. Peripheral blood CD34$^+$ cells comprises of mainly hematopoietic stem cells (HSCs), and putative endothelial progenitor cells. CD34$^+$ cells have been used earlier in cardiac and limb ischemia suggesting thereby the potential of the cells of having cardiovascular properties.

A 6.1-year of median of the follow-up of the study, subjects were divided into groups based on the levels of CD34$^+$ and CD34$^+$CD133$^+$. An analysis was made of the rate of cardiovascular events and the extent of cardiovascular event free survival. The results suggest that the relative CD34$^+$ and CD34$^+$CD133$^+$ cell counts remained significantly lower in patients with cardiovascular events. The associations of absolute CD34$^+$ or CD34$^+$CD133$^+$ cells with cardiovascular outcomes were quantitatively similar but statistically weaker.

The prospective design of the study remains a strength for the study as such studies are

scarce in this domain of the peripheral blood progenitor cell levels and its association with cardiovascular events.

A small number of events 4.5 per 100 patient-years (a total of 48 events—3 cardiovascular deaths, 5 nonfatal strokes, 10 nonfatal acute myocardial infarctions, 16 hospitalizations for heart failure, 6 hospitalizations for unstable angina, and 8 hospitalizations for other cardiovascular causes) makes it difficult to reliably conclude the association between the progenitor cell status and prospective cardiovascular events.

Results from the study suggests that a reduced level of circulating stem cells predicts the occurrence of cardiovascular events in patients with type 2 diabetes mellitus over a period of 6 years. Addition of the stem cell measure improved the existent risk stratification strategy compared with reference models of age, dyslipidemia, neuropathy, peripheral arterial disease, albuminuria, etc.

Mechanistic explanation of peripheral blood progenitor stem cells and cardiovascular events is still sketchy at the best. Whether it represents a bystander of inflammation, hematopoietic expansion, and bone marrow abnormalities, which in turn promote atherosclerosis, is still not quite known. However, the circulating stem cells reflect endogenous regenerative capacity and is probably a mirror of the internal process of aging. Therefore, diabetes, a clinical condition of accelerated aging may harbor the potential reversal of the same, artificially by adding peripheral blood stem cells and modifying the outcome.

2. Plasma Glycated CD59, a Novel Biomarker for Detection of Pregnancy-induced Glucose Intolerance

Ref: Ghosh P, Luque-Fernandez MA, Vaidya A, et al. Plasma glycated CD59, a novel biomarker for detection of pregnancy-induced glucose intolerance. Diabetes Care. 2017;40(7):981–4.

ABSTRACT

Objective: Plasma glycated CD59 (pGCD59) is an emerging biomarker in diabetes. We assessed whether pGCD59 could predict the following: the results of the glucose challenge test (GCT) for screening of gestational diabetes mellitus (GDM) (primary analysis); and the diagnosis of GDM and prevalence of large for gestational age (LGA) newborns (secondary analyses).

Research Design and Methods: Case-control study of 1,000 plasma samples from women receiving standard prenatal care, 500 women having a normal GCT (control subjects) and 500 women with a failed GCT and a subsequent oral glucose tolerance test (case patients).

Results: Compared with control subjects, the median (interquartile range) pGCD59 value was 8.5-fold higher in case patients and 10-fold higher in GDM patients, as follows: control subjects 0.33 (0.19); case patients 2.79 (1.4); GDM patients 3.23 (1.43) ($P < 0.001$); area under the receiver operating characteristic curve 0.92. LGA prevalence was 4.3% in the lowest quartile and 13.5% in the highest quartile of pGCD59.

Conclusions: One pGCD59 measurement during weeks 24-28 identifies pregnancy-induced glucose intolerance with high sensitivity and specificity and can potentially identify the risk for LGA.

Oral glucose challenge test remains the standard method to screen pregnancy induced glucose intolerance. However, the procedure is uncomfortable to the pregnant lady, time consuming, and have poor reproducibility. Nonenzymatic glycation of complement protein CD59 have been found to have the predictive power as a novel biomarker for glycemic status.

Glycated CD59 has been tested for the first time as a glycemic index marker in pregnant population.

Obviously, the major strength of the study is simplicity. If it can be established that glycated CD59 can rival the standard oral glucose challenge test, this would save a large degree of inconvenience to the pregnant population. The high positive and negative predictive values noted in the study are quite inspiring and is likely to interest other investigator to replicate the findings.

This being the first study of this kind with this molecule, this needs to be replicated and established in other populations especially in different ethnicities.

The importance and implication of the study is indeed profound. In case this stands the further tests in different ethnicities, this would be the most sought after screening test for gestational diabetes mellitus for its simplicity and convenience.

A practically implementable marker for glycemic index in pregnant population, however, would need further replication in different parts of the world.

3. Proteomics for Prediction of Disease Progression and Response to Therapy in Diabetic Kidney Disease

Ref: Pena MJ, Mischak H, Heerspink HJ. Proteomics for prediction of disease progression and response to therapy in diabetic kidney disease. Diabetologia. 2016;59(9):1819-31.

ABSTRACT

The past decade has resulted in multiple new findings of potential proteomic biomarkers of diabetic kidney disease (DKD). Many of these biomarkers reflect an important role in the (patho) physiology and biological processes of DKD. Situations in which proteomics could be applied in clinical practice include the identification of individuals at risk of progressive kidney disease and those who would respond well to treatment, in order to tailor therapy for those at highest risk. However, while many proteomic biomarkers have been discovered, and even found to be predictive, most lack rigorous external validation in sufficiently powered studies with renal endpoints. Moreover, studies assessing short-term changes in the proteome for therapy-monitoring purposes are lacking. Collaborations between academia and industry and enhanced interactions with regulatory agencies are needed to design new, sufficiently powered studies to implement proteomics in clinical practice.

The cornerstone of treatment for DKD consists of tight control of blood glucose and blood pressure, preferably with drugs that target the renin-angiotensin-aldosterone system (RAAS). End-stage renal disease is markedly delayed among patients with an initial response to RAAS inhibitors in albuminuria, whereas non-responders showed only a small benefit compared with placebo. Early intervention, prior to organ damage detectable by albuminuria and/or reduced eGFR, would be the best preventative treatment. Therefore a change in the end point is needed to assess the efficacy of intervention. Multiple proteins representing multiple pathways like endothelial dysfunction and inflammation predicted of kidney disease progression in a multiple biomarker study.

Theoretically, proteomics appears an ideal tool to study molecular mechanisms, as it bridges the gap between what is encoded in the genome and its translation into proteins. High-throughput profiling of the proteome permits the assessment of components of proteins within a biological sample. A number of candidate urinary proteomic biomarkers have been identified that can predict kidney disease progression in diabetes. Results from urinary proteomic studies have expanded our pathophysiological knowledge of DKD. Collagen fragments, especially those of the α1 type I collagen chain, have been shown to be significantly altered in urine 3–5 years before the onset of macroalbuminuria.

This being the review article collating the information on this newly emerging field of proteomics in diabetic kidney disease is a veritable source of information.

The newer vista of proteomic profiling of urine in the prediction, diagnosis and risk stratifying of diabetic kidney disease is a welcome tool for the treating clinician.

The knowledge is still in its infancy and needs to be available in a commercial platform for this being useful in a day to day management of patients with diabetes.

4. The Gut Microbiome as a Target for Prevention and Treatment of Hyperglycaemia in Type 2 Diabetes: From Current Human Evidence to Future Possibilities

Ref: Brunkwall L, Orho-Melander M. The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities. Diabetologia. 2017;60(6):943-51.

ABSTRACT

The totality of microbial genomes in the gut exceeds the size of the human genome, having around 500-fold more genes that importantly complement our coding potential. Microbial genes are essential for key metabolic processes, such as the breakdown of indigestible dietary fibers to short-chain fatty acids, biosynthesis of amino acids and vitamins, and production of neurotransmitters and hormones. During the last decade, evidence has accumulated to support a role for gut microbiota (analyzed from fecal samples) in glycemic control and type 2 diabetes. Mechanistic studies in mice support a causal role for gut microbiota in metabolic diseases, although human data favoring causality is insufficient. As it may be challenging to sort the human evidence from the large number of animal studies in the field, there is a need to provide a review of human studies. Thus, the aim of this review is to cover the current and future possibilities and challenges of using the gut microbiota, with its capacity to be modified, in the development of preventive and treatment strategies for hyperglycemia and type 2 diabetes in humans. We discuss what is known about the composition and functionality of human gut microbiota in type 2 diabetes and summarize recent evidence of current treatment strategies that involve, or are based on, modification of gut microbiota (diet, probiotics, metformin and bariatric surgery). We go on to review some potential future gut-based glucose-lowering approaches involving microbiota, including the development of personalized nutrition and probiotic approaches, identification of therapeutic components of probiotics, targeted delivery of propionate in the proximal colon, targeted delivery of metformin in the lower gut, fecal microbiota transplantation, and the incorporation of genetically modified bacteria that express therapeutic factors into microbiota. Finally, future avenues and challenges for understanding the interplay between human nutrition, genetics and microbial genetics, and the need for integration of human multi-omic data (such as genetics, transcriptomics, epigenetics, proteomics and metabolomics) with microbiome data (such as strain-level variation, transcriptomics, proteomics, and metabolomics) to make personalized treatments a successful future reality are discussed.

The importance of the gut microbiota in the development of a multitude of complex human diseases, including type 2 diabetes mellitus (T2DM) cannot be underscored.

Gut microbiome studies are scare in humans, though a lot of information is available in subhuman species. Hence this study which focused on human gut microbiome is of profound importance. There is hardly any consensus regarding which bacteria are significantly altered in T2DM, a common observation has been a decreased abundance of butyrate-producing bacteria with this condition. Drugs also have got a contribution in changing the gut microbiota, e.g., individuals with T2DM who were not treated with metformin had fewer bacteria from genera known to produce butyrate as compared with control participants without diabetes. Moreover, that the previously reported increase in *Lactobacillus species* among T2DM individuals also results from metformin treatment. One novel strategy has also been discussed, like to alter the microbiome is to incorporate genetically modified bacteria that express therapeutic factors into microbiota, i.e., genetically modified microbiota can induce a therapeutic change.

The most important strength is the focus on human studies and collation from multiple resources of information.

The resources for the review were limited by the number of studies. Therefore, the time is still not ripe to reap the benefit to a greater extent.

The clinician needs to appreciate from the study that modified microbiota is responsible for development of diabetes and also the modification of it is likely to lead to amelioration of the illness. Effect of various drugs can be by modifying the microbiota rather than only acting through human cellular receptors as has been noted with metformin.

The area has been under intensive research only for a few recent years and hence the notions, concepts and information on it are gaining momentum to reflect into real life implementation. Needless to mention the scope for future research is immense.

5. Type 2 Diabetes Remission Rates After Laparoscopic Gastric Bypass and Gastric Banding: Results of the Longitudinal Assessment of Bariatric Surgery Study

Ref: Purnell JQ, Selzer F, Wahed AS, Type 2 diabetes remission rates after laparoscopic gastric bypass and gastric banding: Results of the Longitudinal Assessment of Bariatric Surgery Study. Diabetes Care. 2016;39(7):1101-7.

ABSTRACT

Objective: The goals of this study were to determine baseline and postbariatric surgical characteristics associated with type 2 diabetes remission and if, after controlling for differences in weight loss, diabetes remission was greater after Roux-en-Y gastric bypass (RYGBP) than laparoscopic gastric banding (LAGB).

Research Design and Methods: An observational cohort of obese participants was studied using generalized linear mixed models to examine the associations of bariatric surgery type and diabetes remission rates for up to 3 years. Of 2,458 obese participants enrolled, 1,868 (76%) had complete data to assess diabetes status at both baseline and at least one follow-up visit. Of these, 627 participants (34%) were classified with diabetes: 466 underwent RYGBP and 140 underwent LAGB.

Results: After 3 years, 68.7% of RYGBP and 30.2% of LAGB participants were in diabetes remission. Baseline factors associated with diabetes remission included a lower weight for LAGB, greater fasting C-peptide, lower leptin-to-fat mass ratio for RYGBP, and a lower hemoglobin A1c without need for

insulin for both procedures. After both procedures, greater postsurgical weight loss was associated with remission. However, even after controlling for differences in amount of weight lost, relative diabetes remission rates remained nearly twofold higher after RYGBP than LAGB.

Conclusions: Diabetes remission up to 3 years after RYGBP and LAGB was proportionally higher with increasing postsurgical weight loss. However, the nearly twofold greater weight loss-adjusted likelihood of diabetes remission in subjects undergoing RYGBP than LAGB suggests unique mechanisms contributing to improved glucose metabolism beyond weight loss after RYGBP.

Lifestyle and pharmacotherapy can substantially reduce progression from prediabetes to type 2 diabetes mellitus (T2DM). However, remission of diabetes and significant improvement in glycemic control is feasible with bariatric surgery. However, incidence of diabetes tends to increase with time after bariatric surgery, though the rate varies with the type of surgery. Hence, identifying which surgical procedures and patient characteristics are predictive of durable diabetes remission could help clinicians when advising patients regarding the appropriateness of bariatric surgery to treat this condition. Total postoperative weight loss is a significant predictor of diabetes remission after bariatric surgery. And after Roux-en-Y gastric bypass (RYGBP), improvement in hyperglycemia typically occurs rapidly and is thought to be due, in part, to an acute reduction in calorie intake as well as independent gastrointestinal hormonal effects unique to this operation as compared with laparoscopic gastric banding (LAGB).

The study had examined the relationships between degree of weight loss and likelihood of diabetes remission more closely, and found a nearly twofold greater likelihood of diabetes remission after RYGBP compared with LAGB in each year of follow-up, even after accounting for weight loss differences between these procedures. A new metabolic relationship has been identified in the study. The fat adjusted leptin levels after surgery, lower levels of which were identified as a baseline predictor of diabetes remission after RYGBP but not LAGB. It has been suggested that this reduction in leptin-to-fat mass ratio is indicative of enhanced central leptin sensitivity. As leptin has been demonstrated to influence glucose metabolism through mechanisms thought to be mediated by both central and peripheral leptin signaling, it is possible that enhanced leptin sensitivity leads to improved glucose metabolism independent of weight loss after RYGBP.

A large number of subjects being included for this cohort being followed up for a considerable period of time- is an important strength of the study.

As the study was a multicenter, observational cohort study, biases may have been introduced as a result of participants and surgeons electing one surgical procedure over another, by regional variation in surgical approach, and by the fact that the surgical groups did not undergo a formal matching process. Another important drawback was that the surgery types were not randomly assigned and hence this allows some bias to creep in.

The analysis of the entire cohort picks up a number of baseline variables which were linked with higher probability of postoperative diabetes remission, namely younger age, having a higher percent body fat, using fewer noninsulin diabetes medications, not taking insulin, having a shorter duration of a diabetes diagnosis, and who underwent RYGBP surgery. This would help a clinician to decide to choose the type of bariatric surgery needed to achieve optimum result.

A longer follow-up of the cohort is needed to throw more lights on this issue of temporal profile of weight loss and remission of diabetes and any other new adverse events developing. Moreover, a randomized design of the study with proper masking and following a uniform protocol would be needed to reduce the chances of bias in the study.

6. Randomized Trial of a Dual-hormone Artificial Pancreas with Dosing Adjustment During Exercise Compared with No Adjustment and Sensor-augmented Pump Therapy

Ref: Jacobs PG, El Youssef J, Reddy R. Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy. Diabetes Obes Metab. 2016;18(11):1110-9.

ABSTRACT

The authors wanted to examine whether adjusting insulin and glucagon in response to exercise within a dual-hormone artificial pancreas (AP) reduces exercise-related hypoglycemia. The researchers assigned in random order, 21 adults with type 1 diabetes mellitus (T1DM) to underwent three 22-hour experimental sessions: AP with exercise dosing adjustment (APX); AP with no exercise dosing adjustment (APN); and sensor-augmented pump (SAP) therapy. After an overnight stay and 2 hours after breakfast, the participants exercised for 45 minutes at 60% of their maximum heart rate, with no snack given before exercise. During APX, insulin was decreased and glucagon was increased at exercise onset, while during SAP therapy, subjects could adjust dosing before exercise. The two primary outcomes were percentage of time spent in hypoglycemia (<3.9 mmol/L) and percentage of time spent in euglycemia (3.9-10 mmol/L) from the start of exercise to the end of the study. The authors reported an absolute difference of 2.8% less time spent in hypoglycemia for APX versus APN ($p = 0.001$) and 0.5% less time spent in hypoglycemia for APX versus SAP therapy ($p = 0.16$). They found mean time spent in euglycemia to be similar across the different sessions. The authors concluded that adjusting insulin and glucagon delivery at onset of exercise within a dual-hormone AP significantly brings down hypoglycemia compared with no adjustment and performs similarly to SAP therapy when insulin is adjusted before exercise.

Patients with type 1 diabetes mellitus (T1DM), who have little or no insulin secretion and dysfunctional glucagon secretion, are at high risk for both hyperglycemia and hypoglycemia, especially during or after the period of exercise. Artificial pancreas (AP) is comprised of a glucose sensor from which data are collected and streamed into an algorithm (run on a smartphone), which in turn controls delivery from an insulin pump, has been used in T1DM with great success in improving the glycosylated hemoglobin (HbA1c) and rate of hypoglycemia. Dual-hormone APs that deliver glucagon as well as insulin have also shown promise, especially in reducing the chances to develop hypoglycemia.

This was a randomized three-way controlled, cross-over study comparing dual-hormone

Artificial pancreas that adjusted insulin and glucagon dosing during and following exercise (APX), a dual hormone AP that did not adjust dosing based on exercise (APN), and sensor-augmented pump (SAP) therapy. Exercise dosing adjustment within an AP (APX) significantly reduced the percentage of time spent in hypoglycemia compared with no adjustment. There was no statistically significant difference in the baseline glucose of APN and APX. The difference in hypoglycemia primarily occurred after exercise had ended. While hyperglycemia was reduced under the APN arm compared with the SAP and the APX arms, hypoglycemia occurred more often.

Managing exercise-induced hypoglycemia is a challenge to the physician, especially in T1DM who are more commonly likely to be participating in sports activities. This new technology is a shot in the arm of the physician who would benefit from this new technological breakthrough. The other important strength of the study is the crossover design, where each participant spends time in each of the three arms, which reduces bias to a large extent.

One important limitation is obviously the small number of patient, and lack of blinding.

Both these problems, however, were difficult to obviate because of evident reasons. The investigators have reduced the difficulty by designing the study by a crossover study design.

Clinicians can take comfort in the fact that now one proven option is available whereby exercise-induced hypoglycemia may be dealt with more teeth. Moreover, the new option of dual hormone artificial pancreas would open newer vista for treatment.

There is immense scope for future research in this arena, wherein the new option of dual hormone AP can be used in other indications to reduce the chances of hypoglycemia.

7. Angiogenic Effects of Low-intensity Cathodal Direct Current on Ischemic Diabetic Foot Ulcers: A Randomized Controlled Trial

Ref: Asadi MR, Torkaman G, Hedayati M, et al. Angiogenic effects of low-intensity cathodal direct current on ischemic diabetic foot ulcers: A randomized controlled trial. Diabetes Res Clin Pract. 2017;127:147-55.

ABSTRACT

Aims: This study investigated the effect of low-intensity cathodal direct current (CDC) of electrical stimulation (ES) on the release of hypoxic inducible factor-1α (HIF-1α), nitric oxide (NO), vascular endothelial growth factor (VEGF), and soluble VEGF receptor-2 (sVEGFR-2) in the wound fluid of ischemic diabetic foot ulcers (DFUs).

Methods: This study was a randomized, single-blind, placebo-controlled trial. Thirty type 2 diabetes patients with ischemic foot ulcerations were randomly assigned to receive either low-intensity CDC at sensory threshold (ES group, n = 15) or placebo treatment (control group, n = 15) for 1 h/day, 3 days/week, for 4 weeks (12 sessions). After debridement during the first and twelfth treatment sessions, wound fluid was collected before and after ES application to determine the levels of HIF-1α, NO, VEGF, and sVEGFR-2. Wound surface area (WSA) was measured at the first, sixth, and twelfth sessions.

Results: At the first session, after ES application, wound-fluid levels of HIF-1α were significantly increased (+61.98 pg/mL) compared to the control group (−3.85 pg/mL, p = 0.01). After ES application at the first and twelfth sessions, wound-fluid levels of VEGF were also significantly increased (+36.77 and +39.57 pg/mL, respectively) compared to the control group (+4.15 and + 0.15 pg/mL, p = 0.007 and p = 0.019, respectively). There was no significant effect on NO and sVEGFR-2 levels between the groups.

Conclusions: Low-intensity CDC has positive effects on the release of HIF-1α and VEGF in the wound area of ischemic DFUs. Furthermore, our results suggest that applying ES to ischemic DFUs can be a promising way to promote angiogenesis and to achieve better outcomes in diabetic wound healing.

Angiogenesis, an important component of healing is impaired in diabetes, especially in diabetic foot ulcer. Vascular endothelial growth factor (VEGF) and nitric oxide (NO), the two critical component of angiogenesis are downregulated in diabetic foot ulcer. Hypoxic inducible factor-1α (HIF-1α) acts as a crucial stimulator of several angiogenic factors, such as VEGF, FGF-2, and NO, in wound healing. Many studies have reported that the expression of HIF-1α is impaired in diabetic wounds. Decreased HIF-1α in diabetic wounds leads to impaired production of prime angiogenic factors, such as VEGF and NO, in response to hypoxia, which results in reduced neovascularization and an impaired wound healing process in diabetes.

Electrical stimulation (ES) has potential benefits for promoting healing in wounds of various etiologies. ES therapy has been shown to increase skin perfusion, which may be further related to increased expression of VEGF, FGF-2, and NO, resulting in enhanced angiogenesis.

To understand the mechanisms underlying the therapeutic effects of ES on wound healing, it is necessary to examine the cellular and molecular changes that occur in wound sites treated with this physical energy. This study was designed to investigate the release of HIF-1α, NO, VEGF, and sVEGFR-2 in wound fluid after the application of low intensity cathodal direct current in ischemic diabetic foot ulcers, especially its effect in decreasing wound surface area.

There was no significant effect on the wound fluid concentration of VEGF levels, sVEGFR-2 level but the concentration of NO and HIF-1α increased to a significant level. However, most importantly the wound surface area showed a significant diminution in size.

The simple design of the study was a major strength.

Diabetic foot being a very heterogeneous condition, merely including a limited number of patients into it cannot probably reliably provide the data with a small sample size. The study design of single blind trial possibly undermines the strength of the study.

The simple technology of application of low intensity cathodal direct current to improve on the vascular biology in diabetic foot ulcer is indeed a great addition to the armamentarium of the clinician.

The pathophysiology of the putative benefit from this physical process is ill understood. More detailed studies to unravel the pathways of benefit needs to be undertaken.

8. "Let the Algorithm Do the Work": Reduction of Hypoglycemia Using Sensor-augmented Pump Therapy with Predictive Insulin Suspension (SmartGuard) in Pediatric Type 1 Diabetes Patients

Ref: Biester T, Kordonouri O, Holder M, et al. "Let the algorithm do the work": Reduction of hypoglycemia using sensor-augmented pump therapy with predictive insulin suspension (SmartGuard) in pediatric type 1 diabetes patients. Diabetes Technol Ther. 2017;19(3):173-82.

ABSTRACT

Pediatric patients are more prone to hypoglycemia than adult patients with type 1 diabetes mellitus (T1DM). A sensor-augmented insulin pump (SAP) using the MiniMed® 640G system with SmartGuard™ technology allows an automatic stop of insulin delivery based on prediction of low glucose levels. This device may offer additional protection to pediatric patients, beyond conventional sensor-augmented therapy.

In this study, 6 weeks of SAP with SmartGuard™ was compared to a preceding period of 2 weeks with SAP only. The threshold setting for hypoglycemia was 70 mg/dL. Potential reduction in the frequency of hypoglycemic episodes and hypoglycemic intensity were evaluated. A total of 24 pediatric patients with T1DM, with at least 3 months of insulin pump use, were included.

Results demonstrated that SmartGuard™ technology significantly reduced the risk for hypoglycemia in this group of patients, without increasing glycosylated hemoglobin. The best results were achieved when the user did not interfere with pump operation.

Hypoglycemia is a real challenge for the clinicians for treating type 1 diabetes mellitus especially of the pediatric population who may not respond quickly by themselves. The problem is partly mitigated by using the sensor augmented insulin pump. However, even with this the hypoglycemia alert setting in the pump actually determines the effectivity in avoiding hypoglycemia.

This study has compared a machine algorithm of predictive insulin suspension usage with no such usage in the pediatric population.

Simple easy to replicate design of the study makes it clinically very relevant.

A small number of patients being included (6 patients needed to be excluded for protocol violation) limits the importance of the study.

The technological breakthrough of the technology of predictive insulin suspension in the insulin pump will be a welcome advancement in technology which would be useful to prevent frequent hypoglycemia, especially in the pediatric population.

No knowledge gaps identified. The potential scope to improve upon the technology of algorithm based insulin pump administration is huge and can be implemented to improve patient care.

9. A Clinical Trial of the Accuracy and Treatment Experience of the Flash Glucose Monitor FreeStyle Libre in Adults with Type 1 Diabetes

Ref: Ólafsdóttir AF, Attvall S, Sandgren U, et al. A clinical trial of the accuracy and treatment experience of the flash glucose monitor FreeStyle Libre in adults with type 1 diabetes. Diabetes Technol Ther. 2017;19(3):164-72.

ABSTRACT

The FreeStyle Libre, which is a flash glucose monitoring system, became available in the Swedish market in 2014, as a complement to self-monitoring of blood glucose. This study was conducted to evaluate the accuracy of estimating plasma glucose levels in individuals with type 1 diabetes mellitus (T1DM) and treatment experience with the FreeStyle Libre system. A total of 58 adult patients with T1DM used the system for 10–14 days and simultaneously measured capillary blood glucose levels at least six times a day.

The FreeStyle Libre system was associated with an overall mean absolute relative difference 13.2% and a mean absolute difference of 19.8 mg/dL, compared with capillary blood glucose values, indication an overall accuracy that is good along with a high patient satisfaction.

Flash glucose monitoring (FGM) is a small sensor that one wears just under ones skin. It stores the blood glucose levels continuously and one can access them by scanning the sensor.

The accuracy of the FGM technology is measured and the subject's appreciation of the technology and satisfaction with it is calculated. Patient treatment experience is also measured by a questionnaire and reported. The accuracy of the FGM is compared with the well-validated HemoCue technology to assess the accuracy of FGM.

Simplicity of the design of the study remains the important strength of the study.

Using the HemoCue cuvette based measurement technique as the standard undermines the strength of the study, where the gold standard for glucose measurement remains

the hexokinase method in laboratory. Some correlation with the hexokinase would have given more confidence to the study.

The correlation of the HemoCue with the FGM technology has given confidence to the concept of using the FGM technology in a day-to-day clinical care with established accuracy of the FGM technology.

The knowledge gap is minimal and there is undoubtedly a huge potential for future research.

10. Comparison of Insulin Pump Therapy and Multiple Daily Injections Insulin Regimen in Patients with Type 1 Diabetes During Ramadan Fasting

Ref: Alamoudi R, Alsubaiee M, Alqarni A, et al. Comparison of insulin pump therapy and multiple daily injections insulin regimen in patients with type 1 diabetes during Ramadan fasting. Diabetes Technol Ther. 2017;19(6):349-54.

ABSTRACT

Patients with type 1 diabetes mellitus (T1DM), who choose to fast during Ramadan, fall in the high-risk category. An optimum insulin regimen must be opted for, however, data on this limited.

The objective of this study was to compare glycemic profiles, in T1DM patients choosing to fast during Ramadan, who use continuous subcutaneous insulin infusion (CSII) versus those who use multiple daily injections (MDI) of insulin. The primary outcome assessed was rates of hypoglycemia. Secondary outcomes included glycemic control, number of days needed to break fasting, and acute glycemic complications.

Data from self-monitoring of blood glucose and continuous glucose monitoring were collected and compared; and fructosamine levels were evaluated to assess glycemic control.

Results showed no difference in rates of hypoglycemia or hyperglycemia between CSII and MDI. However, CSII was associated with less glycemic variability.

Fasting during Ramadan poses a risk for glycemic deterioration. Both hypoglycemia and hyperglycemia occurs and results in deterioration in the glycemic control. The insulin dependent patients of type 1 diabetes mellitus (T1DM) have compromised glycemic patterns during Ramadan fasting period. The multiple subcutaneous insulin injection (the gold standard) was compared with the insulin pump therapy.

Glucose variability was found to be less in insulin pump compared to MDI. Incidence of mild and severe hypoglycemia are no different between groups. Glycemic variability was also much less in the insulin pump group. Overall insulin pump seems a better option during the period of Ramadan fasting in T1DM.

Simple design of the study remains the important strength of the study.

The small number of patients may be considered a drawback of the study. Otherwise it is a well-designed study.

The clinician may now use this knowledge of better glycemic control with less glycemic variability and hypoglycemia in insulin pump, can confidently use the technology in patients with T1DM during the Ramadan fasting.

The technology of insulin pumps may be used in more number of patients in Ramadan to assess whether it gives a better outcome in T1DM. A further improvement may be considered by using a sensor-augmented pump.

11. Efficacy of the Telemedical Lifestyle Intervention Program TeLiPro in Advanced Stages of Type 2 Diabetes: A Randomized Controlled Trial

Ref: Kempf K, Altpeter B, Berger J, et al. Efficacy of the Telemedical Lifestyle intervention Program TeLiPro in advanced stages of type 2 diabetes: A randomized controlled trial. Diabetes Care. 2017;40(7):863-71.

ABSTRACT

Objective: Lifestyle interventions are the foundation of treatment in newly diagnosed type 2 diabetes mellitus (T2DM). However, their therapeutic potential in advanced disease stages is unknown. We evaluated the efficacy of the Telemedical Lifestyle intervention Program (TeLiPro) in improving metabolic control in advanced-stage T2DM.

Research Design and Methods: In this single-blind, active comparator, intervention study, patients with T2DM [with glycosylated hemoglobin (HbA1c) ≥7.5% (58.5 mmol/mol), and body mass index (BMI) ≥27 kg/m^2 and on ≥2 antidiabetes medications] were recruited in Germany and randomized 1:1 using an electronically generated random list and sealed envelopes into two parallel groups. The data analyst was blinded after assignment. The control group (n = 100) got weighing scales and step counters and remained in routine care. The TeLiPro group (n = 102) additionally received telemedical coaching including medical-mental motivation, a formula diet, and self-monitored blood glucose for 12 weeks. The primary end point was the estimated treatment difference in HbA1c reduction after 12 weeks. All available values per patient (n = 202) were analyzed. Analyses were also performed at 26 and 52 weeks of follow-up.

Results: HbA1c reduction was significantly higher in the TeLiPro group (mean ± SD –1.1 ± 1.2% vs. –0.2 ± 0.8%; p <0.0001). The estimated treatment difference in the fully adjusted model was 0.8% (95% CI 1.1; 0.5) (p <0.0001). Treatment superiority of TeLiPro was maintained during follow-up [week 26: 0.6% [(95% CI 1.0; 0.3), p = 0.0001; week 52: 0.6% [(0.9; 0.2), p <0.001]. The same applies for secondary outcomes: weight (TeLiPro –6.2 ± 4.6 kg vs. control –1.0 ± 3.4 kg), BMI (–2.1 ± 1.5 kg/m^2 vs. –0.3 ± 1.1 kg/m^2), systolic blood pressure (–5.7 ± 15.3 mmHg vs. –1.6 ± 13.8 mmHg), 10-year cardiovascular disease risk, antidiabetes medication, and quality of life and eating behavior (P <0.01 for all). The effects were maintained long-term. No adverse events were reported.

Conclusions: In advanced-stage type 2 diabetes, TeLiPro can improve glycemic control and may offer new options to avoid pharmacological intensification.

Nonpharmacological lifestyle interventions can potentially delay the introduction of pharmacological antidiabetic therapy, reduce the dose of antidiabetic drugs, or even induce remission of the disease in the early stage of the disease.

While similar studies have been undertaken earlier which targeted people with type 2 diabetes mellitus (T2DM) in the early stages, patients with advanced stages of diabetes have rarely been subjected to such telemedical intervention earlier. The Telemedical Lifestyle intervention Program (TeLiPro) is a newly developed 12-week multimodal approach that combines telemonitoring, telemedical coaching, a structured lifestyle intervention program including dietary intervention with a protein-rich meal replacement therapy, self-monitoring of blood glucose, and evaluated mental motivational training. Glycosylated hemoglobin reduction was significantly higher in the TeLiPro group. The estimated treatment difference in the fully adjusted model was 0.8%. Treatment superiority of TeLiPro was maintained during follow-up (week 26: 0.6%; week 52: 0.6%). The same applies for secondary outcomes: weight, body mass index, systolic

blood pressure, 10-year cardiovascular disease risk, antidiabetic medication, and quality of life and eating behavior.

A randomized controlled trial on such a subject where masking would be major issue was conducted especially in an advanced stage of T2DM patients is indeed one important strength of the study.

The results of the study would have been different if it was possible to blind the investigator to the treatment arm allocated to the subject, which of course would be extremely difficult. The modest difference noted

The results from the study suggest that telephonic intervention and frequent contact and continuous training would likely cause a benefit to be derived by the participant with advanced stage of diabetes. It may also open a possibility of intervention in the form of telephonic contact and guiding patients in every stages of diabetes.

The idea of intervention in the form of telephonic contact is novel and at best at nascent stage. However, this novel form of intervention may be difficult to implement but surely worth the effort.

12. Do Mobile Phone Applications Improve Glycemic Control (HbA1c) in the Self-management of Diabetes? A Systematic Review, Meta-analysis, and GRADE of 14 Randomized Trials

Ref: Hou C, Carter B, Hewitt J, et al. Do mobile phone applications improve glycemic control (HbA1c) in the self-management of diabetes? A systematic review, meta-analysis, and GRADE of 14 randomized trials. Diabetes Care. 2016;39(11):2089-95.

ABSTRACT

Objective: To investigate the effect of mobile phone applications (apps) on glycemic control (HbA1c) in the self-management of diabetes.

Research Design and Methods: Relevant studies that were published between 1 January 1996 and 1 June 2015 were searched from five databases: Medline, CINAHL, Cochrane Library, Web of Science, and Embase. Randomized controlled trials that evaluated diabetes apps were included. The authors conducted a systematic review with meta-analysis and GRADE (Grading of Recommendations Assessment, Development and Evaluation) of the evidence.

Results: Participants from 14 studies (n = 1,360) were included and quality assessed. Although there may have been clinical diversity, all type 2 diabetes mellitus studies reported a reduction in HbA1c. The mean reduction in participants using an app compared with control was 0.49% (95% CI 0.30, 0.68; I2 = 10%), with a moderate GRADE of evidence. Subgroup analyses indicated that younger patients were more likely to benefit from the use of diabetes apps, and the effect size was enhanced with health care professional feedback. There was inadequate data to describe the effectiveness of apps for type 1 diabetes mellitus.

Conclusions: Apps may be an effective component to help control glycosylated and could be considered as an adjuvant intervention to the standard self-management for patients with type 2 diabetes mellitus. Given the reported clinical effect, access, and nominal cost of this technology, it is likely to be effective at the population level. The functionality and use of this technology need to be standardized, but policy and guidance are anticipated to improve diabetes self-management care.

The number of people with diabetes is increasing so also the number of people with access to mobile phone and the emerging technology of mobile applications. And there is dire need to improve the quality of care of diabetes. Self-management of the diabetes holds important position in the management of the disease and has shown the potential to improve the outcome.

Due to its ubiquitous, low-cost, interactive, and dynamic health promotion, there is potential for diabetes apps to provide an effective intervention in diabetes self-care. An unbiased view of a number of studies published on this issue has been taken into consideration and a meta-analysis was done. The composite view of these studies suggest that diabetes self-management apps may be an effective component to help control HbA1c and could be considered as an adjuvant intervention to the standard self-management for patients with type 2 diabetes mellitus.

Stringent inclusion and exclusion criteria were applied to conduct the study, and therefore, many studies were excluded limiting the number to a mere 14.

The heterogeneity among the studies is not minimal. There is a large difference of the quality of the trials which are included for the meta-analysis thereby making the conclusion less relevant.

Given the reported clinical effect, access, and nominal cost of this technology, it is likely to be effective at the population level and is likely to be emerging as an effective tool for the clinician to improve the outcome of diabetes treatment.

More number of studies with similar qualities need to be included to make the relevance of the study to be more practical and implementable.