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Diabetes News & Views

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Dia - Do,
bet - your bit,
es - ease :
Do your bit to
make life easy

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Frederick Sanger- does the name tingle a bell?

- Dr. Anupam Prakash

Frederick Sanger passed away at the age of 95 years on November 19, 2013. It tingled a bell when I read in the newspapers that Frederick Sanger passed away. He was a British biochemist and was born on August 13, 1918. When we talk of diabetes, insulin cannot be far away. In fact it is the relative or absolute insulin deficiency which is the basic defect causing diabetes mellitus. The insulin molecule has mesmerised scientists for years together, and does fascinate scientists even today. Frederick Sanger is the person who unravelled the mystery of insulin by determining the structure of insulin. Sanger proved that proteins have a defined chemical composition and for this purpose, he used the 'Sanger reagent', fluorodinitrobenzene (FDNB) to react with the exposed amino groups in the protein. Essentially, Sanger was the first person to reveal the structure of any protein, and that protein molecule happened to be insulin. The discovery was an important step which helped in the laboratory synthesis of insulin and a major advance for diabetes management. Sanger's discovery paved the way for unravelling the mystery of other proteins. Sanger referred to proteins as 'the machinery of living matter'.

Sanger had completed his doctorate (PhD) in 1943. It took him another 10 years and in 1953, he had determined the exact sequence of amino acids for insulin, and also the small differences that existed between insulin of different mammalian species. He was awarded the Nobel Prize in Chemistry in 1958 for this discovery.

This was not all, he continued to work with the other mystifying entity i.e., the nucleic acids and after more than a quarter of a century later, in 1980 was awarded the second Nobel Prize in Chemistry for determination of base sequences in nucleic acids. He deciphered the first DNA whole genome sequence for the virus Phi X 174 and the first human genome in the form of mitochondrial DNA.

Fred Sanger, yes! the name tingled a bell. Such a person is indeed very rare; and to know of such a great person having won two Nobel prizes, giving him elite company are only three people who have won the Nobel Prize twice- Marie Curie (1903 for research on radiation phenomena & 1911 for discovering radium and polonium), Linus Pauling (1954 for the nature of the chemical bond & 1962 Peace prize) and John Bardeen (1956 for invention of transistor & 1972 for theory of superconductivity).

We salute you Fred Sanger! You decoded the insulin for us, and the present day scientists are modifying the same insulin for further benefit of mankind- insulin aspart, insulin lyspro, insulin glargine, insulin detemir, insulin degludec, and probably, the list will continue....

Suggested Reading

1. Frederick Sanger Obituary. Available on http://www.theguardian.com/science/2013/nov/20/frederick-sanger
2. Frederick Sanger. Wikipedia. Available on http://en.wikipedia.org/wiki/Frederick_Sanger

Non-Traditional Risk Factors are Important Contributors to the Racial Disparity in Diabetes Risk: The Atherosclerosis Risk in Communities Study.

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J Gen Intern Med. 2013 Aug 14. [Epub ahead of print]

Background: Traditional risk factors, particularly obesity, do not completely explain the excess risk of diabetes among African Americans compared to whites.

Objective: We sought to quantify the impact of recently identified, non-traditional risk factors on the racial disparity in diabetes risk.

Design: Prospective cohort study.

Participants: We analyzed data from 2,322 African-American and 8,840 white participants without diabetes at baseline from the Atherosclerosis Risk in Communities (ARIC) Study.

Main Measures: We used Cox regression to quantify the association of incident diabetes by race over 9 years of in-person and 17 years of telephone follow-up, adjusting for traditional and non-traditional risk factors based on literature search. We calculated the mediation effect of a covariate as the percent change in the coefficient of race in multivariate models without and with the covariate of interest; 95 % confidence intervals (95 % CI) were calculated using boot-strapping.

Key Results: African American race was independently associated with incident diabetes. Body mass index (BMI), forced vital capacity (FVC), systolic blood pressure, and serum potassium had the greatest explanatory effects for the difference in diabetes risk between races, with mediation effects (95 % CI) of 22.0 % (11.7 %, 42.2 %), 21.7 %(9.5 %, 43.1 %), 17.9 % (10.2 %, 37.4 %) and 17.7 % (8.2 %, 39.4 %), respectively, during 9 years of in-person follow-up, with continued effect over 17 years of telephone follow-up.

Conclusions: Non-traditional risk factors, particularly FVC and serum potassium, are potential mediators of the association between race and diabetes risk. They should be studied further to verify their importance and to determine if they mark causal relationships that can be addressed to reduce the racial disparity in diabetes risk.

PMID: 23943422 [PubMed - as supplied by publisher]

Urinary albumin excretion as a marker of endothelial dysfunction in migraine sufferers: the HUNT study, Norway.

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BMJ Open. 2013 Aug 13;3(8). pii: e003268. doi: 10.1136/bmjopen-2013-003268.

Objective: To investigate urine albumin leakage as a marker of endothelial dysfunction in migraine patients.

Design: A population-based health study.

Participants: 303 patients with migraine, 1009 patients with non-migraine headache and 5287 headache-free controls.

Outcomes: The association between urine albumin- to-creatine ratio (ACR) and headache status was investigated in the Nord-Trøndelag Health Study (HUNT-2). Patients were selected in two strata, based on either (1) self-reported hypertension/diabetes (morbid sample) or (2) a random sample. Analyses were performed using analysis of covariance.

Results: There was no association between headache status and ACR in the study population (p=0.23, mean ACR for migraine 1.66, 95% CI 1.31 to 2.01, for non-migraine headache 1.90, 95% CI 1.71 to 2.09 and for no headache 1.73, 95% CI 1.64 to 1.81) after relevant adjustments. Similarly, no association between headache status and ACR was seen when the analysis was stratified for morbid and random samples, or for migraine with and without aura.

Conclusions: We found no evidence of increased urine albumin leakage in migraine sufferers when compared with headache-free controls. This could indicate that systemic endothelial dysfunction is not a prominent feature of migraine.

PMID: 23943777 [PubMed]

Overview of food products and dietary constituents with antidiabetic properties and their putative mechanisms of action: A natural approach to complement pharmacotherapy in the management of diabetes.

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Mol Nutr Food Res. 2013 Aug 14. doi: 10.1002/mnfr.201300223. [Epub ahead of print]

Diabetes is one of the fastest growing chronic, noncommunicable diseases worldwide. Currently, 11 major classes of pharmacotherapy are available for the management of this metabolic disorder. However, the usage of these drugs is often associated with undesirable side effects, including weight gain and hypoglycemia. There is thus a need for new, safe and effective treatment strategies. Diet is known to play a major role in the prevention and management of diabetes. Numerous studies have reported the putative association of the consumption of specific food products, or their constituents, with the incidence of diabetes, and mounting evidence now suggests that some dietary factors can improve glycemic regulation. Foods and dietary constituents, similar to synthetic drugs, have been shown to modulate hormones, enzymes, and organ systems involved in carbohydrate metabolism. The present article reviews the major classes and modes of action of antidiabetic drugs, and examines the evidence on food products and dietary factors with antidiabetic properties as well as their plausible mechanisms of action. The findings suggest potential use of dietary constituents as a complementary approach to pharmacotherapy in the prevention and/or management of diabetes, but further research is necessary to identify the active components and evaluate their efficacy and safety.

PMID: 23943383 [PubMed - as supplied by publisher]

Urinary Smad1 is a new biomarker for diagnosis and evaluating the severity of diabetic nephropathy.

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Endocrine. 2013 Aug 13. [Epub ahead of print]

The aim of this study was to analyze urinary Smad1 level in patients with type 2 diabetes, explore the possibility of Smad1 being a biomarker for early diagnosis and evaluation of severity of diabetic nephropathy, and explore the impact factors affecting urinary Smad1 concentration. In this study, 132 subjects with type 2 diabetes and 50 healthy volunteers were enrolled. Subjects were grouped according to urine albumin to creatinine ratio (ACR) into: normal albumin in urine (NAU), low albumin in urine (LAU), high albumin in urine (HAU), and very high albumin in urine (VHAU). Among those, LAU, HAU, and VHAU were regarded as the diabetic nephropathy group (DN group), NAU was regarded as nondiabetic nephropathy (non-DN group), and the healthy volunteers were the controls. Enzyme-linked immunosorbent assay was used to detect the urinary Smad1 concentration, urinary Smad1 to creatinine ratio (SCR) was used as the standard reference. Compared with non-DN group, SCR of DN group was higher ($P < 0.05$), while there was no difference between the non-DN group and controls ($P > 0.05$). There was no significant difference for SCR between LAU and NAU groups ($P > 0.05$). The SCR was higher in VHAU group than those in HAU and LAU groups, and higher in HAU than that in LAU group ($P < 0.05$). Pearson correlation analysis showed that SCR measures were positively correlated to ACR, duration and diabetic retinopathy of the disease ($r = 0.285, 0.230, 0.202$; $P = 0.001, 0.008, 0.019$, respectively). Multiple linear regression analysis showed that ACR and duration were independent impact factors for SCR ($P < 0.05$). This is the first known study examining the correlation of Smad1 and DN in clinical practice. It suggested that the urinary Smad1 may be a potential diagnostic parameter for DN and may be used to evaluate the severity of DN. However, it cannot predict those in patients with the earliest DN and low urine albumin concentration. Furthermore, ACR and duration may be independent impact factors for urinary Smad1.

PMID: 23943254 [PubMed - as supplied by publisher]

The Comparison of 24-Hour Urinary Sodium, Albumin, and Protein Excretion in Chronic Kidney Disease Patients with Type 2 Diabetes Mellitus Using Insulin Detemir or Insulin Glargine.

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Clin Drug Investig. 2013 Aug 13. [Epub ahead of print]

Background And Objective: Insulin detemir induces bodyweight loss or less weight gain in patients with type 2 diabetes mellitus. However, in contrast to insulin detemir, insulin glargine has no weight loss effect. Increased sodium excretion has been speculated to be one of the mechanisms of weight loss by insulin detemir. However, there are no studies in the literature comparing sodium excretion between patients using insulin detemir and those using insulin glargine. There are also no studies comparing the excretion of urinary albumin and urinary protein in chronic kidney disease (CKD) patients using insulin detemir or insulin glargine. Thus, the aim of the current study was to compare the effects of insulin detemir and insulin glargine on sodium, albumin, and protein excretion in patients with various stages of CKD and concomitant type 2 diabetes.

Methods: Demographic, clinical, and laboratory data were evaluated for all patients. Hypoglycemic attacks, appetite score, 24-h urinary sodium, albumin, and protein excretion were also measured.

Results: A total of 47 patients (23 taking insulin detemir, 24 taking insulin glargine) were included in the study. There were no differences with respect to 24-h sodium ($p = 0.694$), albumin ($p = 0.297$), or protein excretion ($p = 0.202$) between patient groups. Appetite and hypoglycemic attacks also did not differ between groups. Use of insulin detemir or insulin glargine was not related to sodium, albumin, and protein excretion in stepwise regression analysis.

Conclusion: There was no difference between insulin detemir and insulin glargine with respect to sodium, albumin, and protein excretion in type 2 diabetic CKD patients. Studies are needed both in CKD patients and those with normal renal function to highlight mechanisms regarding the weight loss effect unique to insulin detemir.

PMID: 23943142 [PubMed - as supplied by publisher]

Myopia and diabetes mellitus as modificatory factors of glaucomatous optic neuropathy.

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Jpn J Ophthalmol. 2013 Aug 15. [Epub ahead of print]

Myopic deformation of the eye and metabolic alterations of the nerve tissue of patients with diabetes may modify glaucomatous optic neuropathy (GON). Blockage of axonal transport of neurotrophic factors (NTFs) is the event crucial to understanding the factors that affect GON. The primary, but not sole, blockage site is at the lamina cribrosa (LC). Other than this primary site of damage at the LC, 7 other factors may explain atypical nerve fiber layer (NFL) defects and the vulnerability of the nerve fibers in eyes with high myopia and glaucoma: a second point of blockage at the edge of the posterior scleral foramen; ectatic strain on the NFL; ectasia and distortion of the LC; association of a hypoplastic optic disc; thin and weak collagen fibers; peripapillary chorioretinal atrophy; and myopic neuropathy. Among diabetic patients, diabetic neuropathy in the retinal NFL is present initially, and increased resistance to aqueous outflow leads to ocular hypertension. Superimposition of GON on diabetic neuropathy and ocular hypertension in patients with diabetes may enhance their susceptibility to nerve damage. Results of a meta-analysis study suggested a positive association between diabetes mellitus and glaucoma whereas other reports suggested that leakage of vascular endothelial growth factor, a survival mechanism of ischemic neural tissue, and enhanced stiffness of the LC as a result of diabetic glycation may protect neurons from apoptosis. Thus, modification of GON as a result of diabetes remains controversial.

PMID: 23942995 [PubMed - as supplied by publisher]

Evaluation of a pilot study to influence medication adherence of patients with diabetes mellitus type-2 by the pharmacy.

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Department of General Practice, VU University Medical Center, Amsterdam, The Netherlands.

Int J Clin Pharm. 2013 Aug 13. [Epub ahead of print]

Background Interventions aimed to increase adherence to drug treatment usually are not tailored to the needs of individual patients. A modular pharmacy intervention, named 'Support for Diabetes', was developed to improve adherence to type 2 diabetes treatment. Objective To evaluate the implementation of a new care intervention by using focus groups including pharmacy teams, and assess patient satisfaction. Setting Community pharmacies in The Netherlands Method The intervention comprises a structured patient interview, an intervention guide and modular interventions tailored to the underlying cause of non-adherence. Feasibility was studied in non-adherent type 2 diabetes mellitus patients, and evaluated by means of focus group interviews with pharmacists and pharmacy technicians. Topics included practicability of the patient selection procedure, patient interviews, materials developed for the intervention and general practitioner (GP) co-operation. Patients' experiences (n = 36) were assessed by means of a questionnaire. Main outcome measure Feasibility of the intervention and patients' satisfaction. Results Pharmacists and pharmacy technicians considered the intervention feasible and appreciated its pro-active approach. Involvement of pharmacy technicians proved a stimulating factor. Poor co-operation with GPs and lack of time as well as financial compensation were interfering factors. Patients appreciated the intervention and reported to follow the advice of pharmacists. Conclusion The 'Support for Diabetes' intervention is feasible to implement in pharmacy practice. Poor co-operation between pharmacists and GPs and lack of re-imbursement are obstructions for implementation on a wider scale. These issues should receive attention of pharmacists, policymakers and researchers.

PMID: 23942987 [PubMed - as supplied by publisher]

Thrombotic microangiopathic syndrome: a novel complication of diabetic ketoacidosis.

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Indian Pediatr. 2013 Jul 8;50(7):697-9.

Thrombotic microangiopathic syndrome secondary to diabetic ketoacidosis is an under reported entity in children. We describe 2 girls who developed thrombotic thrombocytopenic purpura (TTP) and thrombocytopenia associated multi organ failure (TAMOF) in new onset diabetes. Both patients presented with classical findings of DKA and were intubated due to low GCS, admitted in PICU and managed according to DKA guidelines. Later on, both patients developed thrombocytopenia, acute kidney injury, and low hemoglobin along with evidence of microangiopathy on peripheral smear. One patient developed paraparesis while other patient had high LDH levels. The clinical diagnosis of TTP and TAMOF was made respectively. Both patients were treated with plasmapharesis and renal replacement therapy. Both gradually improved and were discharged.

PMID: 23942435 [PubMed - in process]

Please note that Email of Delhi Diabetic Forum is now **ddfdelhi1@gmail.com**

The earlier email ddf_delhi@hotmail.com is no longer functional.

Sd/-
Gen. Secretary, DDF

Environmental determinants of islet autoimmunity (ENDIA): a pregnancy to early life cohort study in children at-risk of type 1 diabetes.

Penno MA, Couper JJ, Craig ME, Colman PG, Rawlinson WD, Cotterill AM, Jones TW, Harrison LC.

BMC Pediatr. 2013 Aug 14;13(1):124. [Epub ahead of print]

Background: The incidence of type 1 diabetes has increased worldwide, particularly in younger children and those with lower genetic susceptibility. These observations suggest factors in the modern environment promote pancreatic islet autoimmunity and destruction of insulin-producing beta cells. The Environmental Determinants of Islet Autoimmunity (ENDIA) Study is investigating candidate environmental exposures and gene-environment interactions that may contribute to the development of islet autoimmunity and type 1 diabetes.Methods/design: ENDIA is the only prospective pregnancy/birth cohort study in the Southern Hemisphere investigating the determinants of type 1 diabetes in at-risk children. The study will recruit 1,400 unborn infants or infants less than six months of age with a first-degree relative (i.e. mother, father or sibling) with type 1 diabetes, across five Australian states. Pregnant mothers/infants will be followed prospectively from early pregnancy through childhood to investigate relationships between genotype, the development of islet autoimmunity (and subsequently type 1 diabetes), and prenatal and postnatal environmental factors. ENDIA will evaluate the microbiome, nutrition, bodyweight/composition, metabolome-lipidome, insulin resistance, innate and adaptive immune function and viral infections. A systems biology approach will be used to integrate these. Investigation will be by 3-monthly assessments of the mother during pregnancy, then 3-monthly assessments of the child until 24 months of age and 6-monthly thereafter. The primary outcome measure is persistent islet autoimmunity, defined as the presence of autoantibodies to one or more islet autoantigens on consecutive tests.

Discussion: Defining gene-environment interactions that initiate and/or promote destruction of the insulin-producing beta cells in early life will inform approaches to primary prevention of type 1 diabetes. The strength of ENDIA is the prospective, comprehensive and frequent systems-wide profiling from early pregnancy through to early childhood, to capture dynamic environmental exposures that may shape the development of islet autoimmunity.Trial registration: Australia New Zealand Clinical Trials Registry ACTRN12613000794707.

PMID: 23941366 [PubMed - as supplied by publisher]

Diabetes, physical activity participation and exercise capacity in patients with schizophrenia.

Vancampfort D, De Hert M, Sweers K, De Herdt A, Detraux J, Probst M.
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Psychiatry Clin Neurosci. 2013 Aug 13. doi: 10.1111/pcn.12077. [Epub ahead of print]

Aim: The aim of this study was to determine if in schizophrenia patients the presence of diabetes is associated with lower physical activity participation and lower exercise capacity compared to patients with pre-diabetes and to patients without (pre-) diabetes.

Methods: Schizophrenia patients without (pre-)diabetes (n = 86) were compared with pre-diabetic (n = 10) and diabetic patients (n = 10). Patients were assessed on physical activity participation using the Baecke physical activity questionnaire and on exercise capacity using a 6-min walk test (6MWT).

Results: The three groups were similar in age, sex, mean antipsychotic medication dose, negative and depressive symptoms and smoking behavior. Distance achieved on the 6MWT, however, was approximately 15% shorter ($P < 0.05$) in patients withdiabetes than in patients without (pre-)diabetes (500.3 ± 76.9 m vs 590.7 ± 101.8 m). Patients with diabetes were also significantly less physically active ($P < 0.05$). No differences between diabetic and pre-diabetic patients were found. Pre-diabetic patients had a higher body mass index (BMI) than non-diabetic patients (30.0 ± 7.3 vs 24.3 ± 4.3, $P < 0.05$). An interaction effect with BMI for differences in Baecke ($F = 29.9$, $P < 0.001$) and 6MWT ($F = 13.0$, $P < 0.001$) scores was seen between diabetic and non-diabetic patients on univariate ANCOVA.

Conclusion: The additive burden of diabetes might place patients with schizophrenia at an even greater risk for functional limitations in daily life.

Secondary Analysis of Publicly Available Data Reveals Superoxide and Oxygen Radical Pathways are Enriched for Associations Between Type 2 Diabetes and Low-Frequency Variants.

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British Columbia Clinical Genomics Network, University of British Columbia, Vancouver, British Columbia, Canada; Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada; Child and Family Research Institute, University of British Columbia, Vancouver, British Columbia, Canada.

Genome-wide association studies explain at most 5%-10% of the heritable components of type 2 diabetes. Some of the "missing type 2 diabetes heritability" could be explained by low-frequency variants. We examined the associations between low-frequency variants and type 2 diabetes, using data from 2538 diabetic and 2977 nondiabetic subjects in the publicly available database of Genotypes and Phenotypes. We applied two approaches. First, we combined information from all low-frequency (1%-5%) variants at a locus in a gene-centric analysis of associations with diabetes. Next, we searched for gene ontology (GO) biological processes that were enriched for gene-centric associations, after correcting for multiple testing to control the false discovery rate (FDR). We found three GO biological processes that were significantly enriched for associations to diabetes: "response to superoxide" (FDR-adjusted p = 2.7 × 10(-3)), "response to oxygen radical" (FDR-adjusted p = 2.7 × 10(-3)), and "heart contraction" (FDR-adjusted p = 2.6 × 10(-2)). There were three genes that contributed to "response to superoxide" and "oxygen radical" pathways, including the SOD1 gene. Gene-centric tests of association with low-frequency variants, followed by analysis to evaluate which biological pathways are enriched for these associations has the potential to recover, at least some proportion of, the "missing heritability" of type 2 diabetes.

PMID: 23941231 [PubMed - as supplied by publisher]

Hyperfiltration in normoalbuminuric type 1 diabetic patients: relationship with urinary albumin excretion rate.

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Coll Antropol. 2013 Jun;37(2):471-6.

Hyperfiltration has been documented in type 1 diabetes and may contribute to the high risk for development of albuminuria and progression of nephropathy. However, recent studies suggest that the risk of progression to albuminuria in type 1 diabetes was not increased by hyperfiltration. We investigated associations of estimated glomerular filtration rate (eGFR) and urinary albumin excretion rate (UAE) in normoalbuminuric type 1 diabetic patients. Study included 313 normoalbuminuric patients with type 1 diabetes, none showed signs of adrenal, renal, or cardiovascular diseases. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Glomerular hyperfiltration was defined as eGFR > or = 125 mL min(-1) 1.73 m(-2). Renal hyperfiltration was present in 12% of the study group. Subjects with eGFR > or = 125 mL min(-1) 1.73 m(-2) were younger, had shorter duration of diabetes, lower levels of total and LDL cholesterol, and higher HbA1c than subjects with an eGFR below 125 mL min(-1) 1.73 m(-2). Type 1 diabetic patients with hyperfiltration also had significantly lower UAE. In a multiple logistic regression analysis, higher eGFR was associated with lower UAE. Our results indicate that normoalbuminuric type 1 diabetic patients with hyperfiltration have lower UAE than those with renal function in the normal range. Together with other recent studies this may suggest that creatinine-based estimates of GFR indicating hyperfiltration is not associated with higher UAE and subsequent development of microalbuminuria.

PMID: 23940992 [PubMed - in process]

Association of lipoprotein levels with mortality in subjects aged 50 + without previous diabetes or cardiovascular disease: A population-based register study.

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Department of Clinical Biochemistry, Slagelse Hospital, Region Zealand, Denmark.

Scand J Prim Health Care. 2013 Sep;31(3):172-80. doi:10.3109/02813432.2013.824157.

Abstract Objective. This study aimed to investigate the association of lipoprotein and triglyceride levels with all-cause mortality in a population free from diabetes and cardiovascular disease (CVD) at baseline. The European Guidelines on cardiovascular disease prevention state that in general total cholesterol (TC) should be < 5 mmol/L (190 mg/dL) and low-density lipoprotein cholesterol (LDL-C) should be < 3 mmol/L (115 mg/dL). Design. A population-based register study in the period 1999-2007 including 118 160 subjects aged 50 + without statin use at baseline. All-cause mortality was related to lipoprotein and triglyceride levels and adjusted for statin use after inclusion.

Results. All-cause mortality was lower in the groups with TC or LDL-C above the recommended levels. Compared with subjects with TC < 5 mmol/L, adjusted hazard ratios for the group aged 60-70 years ranged from 0.68 (95% confidence interval (CI) 0.61-0.77) for TC 5-5.99 mmol/L to 0.67 (95% CI 0.59-0.75) for TC 6-7.99 mmol/L and 1.02 (95% CI 0.68-1.53) for TC ≥8 mmol/L in males and from 0.57 (95% CI 0.48-0.67) to 0.59 (95% CI 0.50-0.68) and 1.02 (95% CI: 0.77-1.37) in females. For triglycerides, ratios compared with the group < 1 mmol/L in the females aged 60-70 years ranged from 1.04 (95% CI 0.88-1.23) to 1.35 (95% CI 1.10-1.66) and 1.25 (95% CI 1.05-1.48) for triglycerides 1-1.39 mmol/L, 1.4-1.69 mmol/L, and ≥1.7 mmol/L, respectively. Statin treatment after inclusion provided a survival benefit.

Conclusion. These associations indicate that high lipoprotein levels do not seem to be definitely harmful in the general population. However, high triglyceride levels in females are associated with decreased survival.

PMID: 23941088 [PubMed - in process]

Caveolin-1 upregulation in diabetic fibroblasts and wounded tissues: implication for understanding the underlying mechanisms of non-healing diabetic ulcers.

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Am J Physiol Endocrinol Metab. 2013 Aug 13. [Epub ahead of print]

A heightened state of oxidative stress and senescence of fibroblasts constitute potential therapeutic targets in non-healing diabetic wounds. Here, we studied the underlying mechanism mediating diabetes-induced cellular senescence using in vitro cultured dermal fibroblasts and in vivo circular wounds. Our results demonstrated that the total antioxidant capacity, mRNA levels of thioredoxinreductase and glucose-6-phosphate dehydrogenase as well as the ratio of NADPH/NADP were markedly decreased in fibroblasts from patients with type 2 diabetes (Dfs). Consistent with this shifts in favor of excessive reactive oxygen species, DFs also displayed a significant increase in senescence-associated β-galactosidase activity and phospho- histone H2AX (pH2AX) level. Moreover, the ability of PDGF to promote cell proliferation/migration and to regulate the phosphorylation-dependent activation of Akt and ERK1/2 appear to be attenuated as a function of diabetes. Mechanistically, we found that diabetes-induced oxidative stress up-regulated caveolin-1 (Cav-1) and PTRF expression, which in turn sequestered Mdm2 away from p53. This process resulted in the activation of a p53/p21-dependent pathway and the induction of premature senescence in DFs. Most of the aforementioned oxidative stress and senescence-based features observed in DFs were recapitulated in a 10-day-old diabetic wound. Intriguingly, we confirmed that the targeted depletion of Cav-1 or PTRF using siRNA- or Vivo-Morpholino antisense-based gene therapy markedly inhibited diabetes/oxidative stress-induced premature senescence and also accelerated tissue repair in this disease state. Overall, our data illuminate Cav-1/PTRF-1 as a key player of a novel signaling pathway that may link a heightened state of oxidative stress to cellular senescence and impaired wound healing in diabetes.

PMID: 23941874 [PubMed - as supplied by publisher]