List of ten best papers and highlighted important discoveries/ contributions

Paper 1. Dutta S, Tarafdar S, Mukhopadhyay P, Bhattacharyya NP, Ghosh S. Plasma Cell-Free DNA to Differentiate Malignant from Benign Thyroid Nodules. J Clin Endocrinol Metab. 2021 Apr 23;106(5):e2262-e2270. doi: 10.1210/clinem/dgab030.

Background: Molecular testing is increasingly used to identify malignancy in thyroid nodules (especially indeterminate category). Measurement of cell-free DNA (cfDNA) levels from plasma has been useful in diagnosis of cancers of other organs/tissues; herein we analyze cfDNA levels in patients with thyroid nodules to explore the possibility of establishing a cutoff for identification of malignancy.

Methods: Patients underwent ultrasonography (USG) and USG-guided fine needle aspiration as well as surgery, where indicated. Cell-free DNA was extracted from plasma and quantified. In initial analysis (determination of cutoff), cfDNA levels were compared between Bethesda 2 and Bethesda 5 &6 to establish a cutoff value that could differentiate malignant from benign nodules. In the subsequent analysis, the aforementioned cutoff was applied (validation of cutoff) to those with indeterminate nodules to check ability to predict malignancy.

Results: Fine needle aspiration (n = 119) yielded patients with Bethesda 2 (n = 69) Bethesda 5 & 6 (n = 13) who underwent histopathological confirmation. Cell-free DNA levels in these 2 groups were 22.85 ± 1.27 and 96.20 ± 8.31 (ng/mL) respectively. A cfDNA cutoff of 67.9 ng/mL, with area under the curve of 0.992 (95% CI, 0.97-1.0) with 100% sensitivity and 93% specificity was established to identify malignant lesions. Indeterminate group (Bethesda 3 & 4) underwent surgery (malignant n = 24), (benign n = 13), and using the previously identified cutoff for cfDNA, we were able to identify malignant lesions with a sensitivity of 100% and specificity of 92.3%. There was a very strong agreement between cfDNA-based classification with histopathology-based classification of benign and malignant nodules (Cohen's kappa 0.94; $P < 0.001$).

Conclusion: Plasma cfDNA estimation could help differentiate malignant from benign thyroid nodules.

Paper 2. Neogi S, Mukhopadhyay P, Sarkar N, Datta PK, Basu M, Ghosh S. Overt and Subclinical Adrenal Insufficiency in Pulmonary Tuberculosis. Endocr Pract. 2021 Jun;27(6):601-606. doi: 10.1016/j.eprac.2020.11.012.

Objective: Though gingivitis is common in children with type 1 diabetes mellitus (T1DM), the overall periodontal health in T1DM during the pubertal stage is less well-characterized. The study was undertaken to explore the possible influence of puberty and metabolic derangement on periodontal health in T1DM.

Methods: In this cross-sectional study, 110 subjects between 10-18 years with T1DM and 52 healthy siblings of similar age were evaluated for pubertal stage, glycosylated hemoglobin (HbA1c), and periodontal health. Simplified oral hygiene index (OHIS), gingival index (GI),

plaque index (PI), bleeding on probing (BOP), and probing depth (PPD) were evaluated at 4 sites per tooth as per 6 Ramfjord index teeth used to assess periodontal disease (PD).

Results: PD not merely gingivitis was significantly higher in T1DM (84/110, 76.36%) than the control group (28/52, 53.8%) (P = .004). Irrespective of pubertal status, children with T1DM had worse GI, PI, BOP, and PPD than nondiabetic subjects, although OHIS was better in diabetes. In both T1DM and nondiabetic subjects, pubertal subjects showed significantly worse OHIS, PPD, BOP, and GI than prepubertal subjects. PD was correlated with pubertal stage, age, and HbA1c, although less strongly with the duration of diabetes. In logistic regression, pubertal stage was a stronger predictor of PD (OR = 14.26) than age (OR = 2.22), and HbA1c (OR = 1.5) rather than the presence of diabetes and its duration.

Conclusions: Though pubertal status, age, and poor glycemic control rather than the presence of diabetes and its duration are associated with gingivitis and other forms of PD, puberty had a more profound effect in the pathogenesis of PD in T1DM.

Paper 3. Chakraborty P, Mukhopadhyay P, Bhattacharjee K, Chakraborty A, Chowdhury S, Ghosh S. Periodontal Disease in Type 1 Diabetes Mellitus: Influence of Pubertal Stage and Glycemic Control. Endocr Pract. 2021 Aug; 27(8):765-768. doi: 10.1016/j.eprac.2021.01.010.

Objective: Though gingivitis is common in children with type 1 diabetes mellitus (T1DM), the overall periodontal health in T1DM during the pubertal stage is less well-characterized. The study was undertaken to explore the possible influence of puberty and metabolic derangement on periodontal health in T1DM.

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Paper 4. Mandal S, Mukhopadhyay P, Ghosh S. Sexual dysfunctions in Sheehan's syndrome. Endocr Pract. 2021 Jul 23:S1530-891X(21)01147-2. doi: 10.1016/j.eprac.2021.07.013.

Background: Sheehan's syndrome (SS) is not an uncommon cause of hypopituitarism in developing countries. Lack of sex-steroids both from ovaries and adrenals could lead to sexual dysfunction in SS. Sexual function is a neglected aspect of health in women in developing countries, though it contributes greatly towards quality of life and feeling of well being. Objective documentation of sexual function in SS is limited.

Materials and Methods: Thirty two subjects with SS on conventional therapy (except Growth Hormone) were evaluated. SS was diagnosed as per standard criteria. Sexual function was assessed by validated questionnaires using Female Sexual Function Index (FSFI). Thirty healthy women of similar age range and socio-economic background were included as comparators.

Results: Mean age (±SD) of study population and healthy controls were 39.9 (±8.6) and 38.2 (±6.8) years respectively. Median (IQR) interval between inciting event and diagnosis of SS was 8.3 (5.2-13.5) years. Thirty subjects were active sexually. Twenty eight (93%) had sexual dysfunction i.e. FSFI score ≤ 26.55. Median total FSFI scores in SS and controls were 20.8 and 29.05 respectively (p=0.001). There was statistically significant difference for individual parameter of sexual function i.e. desire, arousal, lubrication, orgasm and satisfaction between SS and controls. However pain during intercourse was not different. FSFI score in SS was not correlated with any of the endocrine parameters or duration of the disease since diagnosis.

Conclusion: Sexual dysfunction is very common affecting more than 90% of subjects with SS.

Paper 5. Bhat S, Mukhopadhyay P, Raychaudhury A, Chowdhury S, Ghosh S. Predictors of hypopituitarism due to vasculotoxic snake bite with acute kidney injury. Pituitary. 2019 Dec;22(6):594-600. doi: 10.1007/s11102-019-00990-8.

Purpose: Hypopituitarism frequently develops following vasculotoxic snake bite complicated by acute kidney injury (AKI). Well defined prospective studies of prevalence of hypopituitarism and its predictors in vasculotoxic snake bites complicated by AKI are unavailable.

Methods: Fifty-one consecutive patients of AKI following vasculotoxic snake bite were evaluated for various clinical/biochemical parameters (including Free T4, TSH, Cortisol, ACTH, total testosterone, FSH, LH, prolactin, and IGF-1). Diabetes insipidus was evaluated in relevant cases. Twenty minutes whole blood clotting time (WBCT) at presentation was measured in all. MRI of hypothalamo-pituitary region was done at 3 months in subjects with hypopituitarism to rule out structural lesion.

Results: 21.6% (11/51) patients developed hypopituitarism at baseline (within 7 days), 39.3% (13 /33) at 3 months developed hypopituitarism. Cortisol deficiency was the commonest abnormality. Subjects who developed hypopituitarism at baseline were younger compared to those without hypopituitarism (35.67 years vs. 46.59 years, p = 0.032) and required more sessions of hemodialysis (8 vs. 3, p = 0.041). Binary logistic regression confirmed that

development of hypopituitarism could be predicted by increased number of sessions of hemodialysis (OR 1.51, p = 0.008) and 20 min WBCT (OR 1.2, p = 0.038).

Conclusion: Hypopituitarism is common following vasculotoxic snake bite in subjects who develop AKI requiring hemodialysis. Hypopituitarism can develop as early as 7 days following snake bite and should be evaluated for particularly in younger subjects, especially those requiring increasing number of sessions of hemodialysis and in subjects with abnormal 20 min WBCT at presentation.

Paper 6. Ghosh S, Pramanik S, Biswas K, Bhattacharjee K, Sarkar R, Chowdhury S, Mukhopadhyay P. Levothyroxine Absorption Test to Differentiate Pseudomalabsorption from True Malabsorption. Eur Thyroid J. 2020 Jan;9(1):19-24. doi: 10.1159/000504218. Epub 2019 Nov 20.

Background: The levothyroxine absorption test for evaluation of pseudomalabsorption in patients with primary hypothyroid is not standardised. An individual in whom a workup for malabsorption is warranted remains undefined.

Methods: Twenty-five euthyroid, 25 newly diagnosed hypothyroid, 25 treated hypothyroid with normalised TSH, and 25 hypothyroid subjects with elevated TSH despite adequate dose of levothyroxine for more than 6 months, and 10 euthyroid subjects with true malabsorption were administered levothyroxine (10 μg/kg or maximum 600 μg) to study its absorption profile by measuring free T4 level at hourly intervals for 5 h.

Results: Free T4 peaked at 3 h with marginal insignificant decline at 4 h in all groups. The increments of free T4 (between baseline and 3 h) of the four groups (except malabsorption) were not statistically different. The mean increment of free T4 in true malabsorption was 0.39 ng/dL (95% CI: 0.29–0.52) and it was 0.78 ng/dL (95% CI: 0.73–0.85) (10.4 pmol/L) for other groups combined together. The cut off of free T4 increment at 3 h from baseline above 0.40 ng/dL had a sensitivity of 97% and specificity of 80% (AUC 0.904, p < 0.001) to exclude true malabsorption.
Conclusion: Subjects with elevated TSH on adequate dose of LT4 can be reliably diagnosed to be non-adherent to treatment with levothyroxine absorption test. The incremental value above 0.40 ng/dL (5.14 pmol/L) at 3 h may be useful to identify individuals where workup of malabsorption is unwarranted.

Paper 7. Ghosh S, Mukhopadhyay P, Pandey P, Chatterjee P, Pandit K. Cardiovascular safety of Glimepiride: An indirect comparison from CAROLINA and CARMELINA. Diab Vasc Dis Res. 2020 Nov-Dec;17(6):1479164120973653. doi: 10.1177/1479164120973653.

Background: Despite having unquestionable glucose lowering efficacy, current guidelines no more favour the uses of sulphonylureas for CV safety concern, except when cost is an issue. However, formal cardiovascular outcome trial (CVOT) is not available.

Materials and methods: We performed an indirect treatment comparison to find the hazard ratio for 3-point MACE, all-cause death, CV death and non-CV death between glimepiride and

placebo based on two large CVOTs which established the CV safety of linagliptin (CARMELINA and CAROLINA).

Results: Glimepiride was shown to have a non-inferior risk compared to placebo for 3-point MACE (HR 1.04, 95% CI 0.850, 1.274), all-cause mortality (HR 1.08, 95% CI 0.880, 1.317), CV death (HR 0.96, 95% CI 0.732, 1.259), and non-CV death (HR 1.24, 95% CI 0.893, 1.733).

Conclusion: Cardiovascular safety of glimepiride is re-assuring and may help patients with type 2 diabetes world-over to avail the benefit of this affordable efficacious medication.

Paper 8. Ghosh S, Waugh N. Mortality risk remains higher in individuals with type 1 diabetes: A population-based cohort study (the Ayrshire diabetes follow-up cohort [ADOC]). Diabetes Obes Metab. 2018 Aug;20(8):1965-1971. doi: 10.1111/dom.13334. Epub 2018 May 29. PMID: 29687581.

Aims: Type 1 diabetes is associated with an increased risk of cardiovascular disease and allcause mortality. Numerous studies have demonstrated that outcomes for diabetes are improved by intensive glycaemic control, blood pressure control, and treatment of dyslipidaemia in addition to cessation of smoking. The aim of this study was to compare mortalities in individuals with type 1 diabetes with that in non-diabetic individuals, and to investigate the effects of age, gender, glycaemic control, socio-economic status, hypertension, ischaemic heart disease (IHD), smoking status, body mass index (BMI) and dyslipidaemia.

Methods: A population-based analysis in Ayrshire and Arran, Scotland included 253 304 nondiabetic individuals and 1324 individuals with type 1 diabetes who were tracked from 2009 to 2014.

Results: Patients with type 1 diabetes had higher mortality rates than non-diabetic individuals (HR, 3.20; $P < .01$), with relative mortality in female individuals with type 1 diabetes being higher than that in males (OR, 2.38 vs 1.52; $P < .01$). Increasing age (HR, 2.37), smoking (HR, 1.85), IHD (HR, 1.62) and hypertension (HR, 1.21) (all $P < .01$) increased mortality risk. A hypertensive female with type 1 diabetes and IHD who smoked had an HR of 11.6 compared with a nonsmoking, normotensive non-diabetic female without IHD. For a hypertensive male with type 1 diabetes and IHD who smoked, HR was 6.96. BMI > 30 kg/m2 was associated with reduced mortality risk in both non-diabetic (HR, 0.61) and diabetic subjects (HR, 0.40).

Conclusions: This study confirmed that the risk of mortality in individuals with type 1 diabetes remains elevated. Further studies are required to understand how gender affects the disparity in mortality and why obesity appears to be protective.

Paper 9. Sarkar, J., Nargis, T., Tantia, O., Ghosh, S., & Chakrabarti, P. (2019). Increased Plasma Dipeptidyl Peptidase-4 (DPP4) Activity Is an Obesity-Independent Parameter for Glycemic Deregulation in Type 2 Diabetes Patients. Frontiers in endocrinology, 10, 505. https://doi.org/10.3389/fendo.2019.00505

Background: Increase in circulating dipeptidyl peptidase-4 (DPP4) activity and levels has been reported to associate both with hyperglycemia and obesity. Here we aim to decipher the role of enhanced plasma DPP4 activity in obese type 2 diabetes (T2DM) patients.

Materials and methods: Plasma DPP4 levels and activity were measured in obese and non-obese newly diagnosed T2DM patients (n = 123). Visceral and subcutaneous adipose tissue DPP4 expression and activity were determined in 43 obese subjects (T2DM = 21 and non-T2DM = 22). 20 subjects undergoing Mini-Gastric Bypass (MGB) surgery were followed up over 4–6 weeks for plasma DPP4.

Results: Plasma DPP4 levels and activity both were increased in T2DM patients compared to control group. However, DPP4 levels and not DPP4 activity were increased in obese T2DM patients compared to non-obese T2DM (62.49 ± 26.27 μg/ml vs. 48.4 ± 30.98 μg/ml, respectively, p = 0.028). DPP4 activity in visceral adipose tissue (VAT) from obese T2DM and obese non-T2DM groups were similar (5.05 ± 3.96 nmol/min/ml vs. 5.83 ± 4.13 nmol/min/ml respectively, p = 0.548) in spite of having increased DPP4 expression in the obese T2DM group. Moreover, in obese patients, plasma DPP4 levels and activity did not show any significant change after weight reduction and glycemic control following MGB surgery.

Conclusion: Enhanced plasma DPP4 activity in T2DM occurs independently of obesity. Thus, adipose derived DPP4 may not be playing any significant role in glycemic deregulation in obese T2DM patients.

Paper 10: Ghosh I, Mukhopadhyay P, Das K, Anne M B, Ali Mondal S, Basu M, Nargis T, Pandit K, Chakrabarti P, Ghosh S. Incretins in fibrocalculous pancreatic diabetes: A unique subtype of pancreatogenic diabetes. J Diabetes. 2021 Jun;13(6):506-511. doi: 10.1111/1753-0407.13139.

Background: Studies evaluating endocrine and exocrine functions in fibrocalculous pancreatic diabetes (FCPD) are scarce.

Methods: Insulin, C-peptide, glucagon, incretin hormones (glucagon-like peptide 1 [GLP-1] and gastric inhibitory peptide [GIP]), and dipeptidyl peptidase IV (DPP-IV) were estimated in patients with FCPD (n = 20), type 2 diabetes mellitus (T2DM) (n = 20), and controls (n = 20) in fasting and 60 minutes after 75 g glucose.

Results: Fasting and post-glucose C-peptide and insulin in FCPD were lower than that of T2DM and controls. Plasma glucagon decreased after glucose load in controls (3.72, 2.29), but increased in T2DM (4.01, 5.73), and remained unchanged in FCPD (3.44, 3.44). Active GLP-1 (pmol/L) after glucose load increased in FCPD (6.14 to 9.72, P = <.001), in T2DM (2.87 to 4.62, P < .001), and in controls (3.91 to 6.13, P < .001). Median active GLP-1 in FCPD, both in fasting and post-glucose state (6.14, 9.72), was twice that of T2DM (2.87, 4.62) and 1.5 times that of controls (3.91, 6.13) (P < .001 for all). Post-glucose GIP (pmol/L) increased in all: FCPD (15.83 to 94.14), T2DM (21.85 to 88.29), and control (13.00 to 74.65) (P < .001 for all). GIP was not different between groups. DPP-IV concentration (ng/mL) increased in controls (1578.54,

3012.00) and FCPD (1609.95, 1995.42), but not in T2DM (1204.50, 1939.50) (P = .131). DPP-IV between the three groups was not different. Fecal elastase was low in FCPD compared with T2DM controls.

Conclusions: In FCPD, basal C-peptide and glucagon are low, and glucagon does not increase after glucose load. GLP-1, but not GIP, in FCPD increases 1.5 to 2 times as compared with T2DM and controls (fasting and post glucose) without differences in DPP-IV.