List of ten best papers and highlighted important discoveries/ contributions

Paper 1. Dutta S, Tarafdar S, Mukhopadhyay P, Bhattacharyya NP, Ghosh S. Detection of driver mutations in plasma cell-free nucleic acids in differentiated thyroid neoplasm. Eur J Endocrinol. 2023;188(1):lvac018. doi:10.1093/ejendo/lvac018

Importance: This proof-of-concept paper demonstrates that driver mutations can be detected in plasma in differentiated thyroid tumors, and we were able to detect mutations in upto 80% malignant thyroid nodules. Additionally, cancer subtypes could also be predicted using a 8-gene panel. In almost 90% follicular adenoma, rat sarcoma virus (RAS) mutations were detectable. There was a strong agreement between driver mutations found in plasma samples, FNAC materials, and histopathology samples. This has potential as a noninvasive, preoperative diagnostic tool (particularly of clinical importance in indeterminate nodules) and may help in detection of residual tumor after surgery. Future research is warranted to test the role of this tool to detect tumor recurrence.

Objective: Ultrasonographic (USG) evaluation and fine-needle aspiration (FNA) are cornerstone for evaluation of thyroid neoplasm. Molecular technique including detection of driver mutation from FNA cytology (FNAC) material is an established modality. In this study, we explored the feasibility of using plasma cell-free nucleic acids to identify known driver mutations in differentiated thyroid neoplasm.

Design: Patients presenting with thyroid nodules underwent USG with Thyroid Image Reporting and Data Systems scoring and FNAC (Bethesda classification). All patients in Bethesda 3, 4, 5, 6 underwent surgery and histopathological confirmation. Patients in Bethesda 2 (cosmetic concerns, compressive symptoms) underwent surgery, and rests were presumed benign on the basis of USG, FNAC features, and clinical follow-up) **Study Setting:** Endocrinology clinic.

Participants: Subjects with thyroid nodule.

Main outcome(s) and measure(s): Plasma sample, FNA, and histopathology material were evaluated for driver mutations (8-gene panel comprising BRAF-V600E, RET/PTC3, RET/PTC1, TERT promoter, HRAS, NRAS, KRAS, and PAX8-PPARG).

Results: A total of 223 subjects were recruited; of these 154 were benign and 69 had differentiated thyroid cancer. We were able to detect driver mutation from plasma in 55 subjects (79.71%) of all malignant patients, and 11 patients in benign category had RAS mutation (follicular adenoma). Rest of the benign nodules did not have any detectable driver mutations.

Conclusions and relevance: Plasma might be a viable noninvasive alternative source for detection of driver mutations (8-gene panel) in subjects with differentiated thyroid tumors and may have significant clinical utility.

Paper 2. 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 3. Basu M, Pulai S, Neogi S, et alPrevalence of non-diabetic kidney disease and inability of clinical predictors to differentiate it from diabetic kidney disease: results from a prospectively performed renal biopsy studyBMJ Open Diabetes Research and Care 2022;10:e003058. doi: 10.1136/bmjdrc-2022-003058

Introduction: Renal involvement in type 2 diabetes mellitus (T2DM) may be due to diabetes (diabetic kidney disease (DKD)), causes other than diabetes (non-diabetic kidney disease (NDKD)) or overlap of DKD and NDKD (mixed kidney disease group). Prevalence of NDKD and predictive value of clinical or biochemical indicators have been explored in retrospective cohorts with preselection biases warranting the need for prospectively conducted unbiased renal biopsy study.

Research design and methods: Consecutive subjects aged >18 years with T2DM and renal involvement with estimated glomerular filtration rate of 30–60 mL/min/m2 and/or albumin:creatinine ratio of >300 mg/g were offered renal biopsy. Prevalence of DKD, NDKD and mixed kidney disease was documented. Clinical/laboratory parameters of subjects were recorded and compared between groups and were tested for ability to predict histopathological diagnosis.

Results: We screened 6247 subjects with T2DM of which 869 fulfilled inclusion criteria for biopsy. Of the 869 subjects, biopsy was feasible in 818 subjects. Out of 818, we recruited first 110 subjects who agreed to undergo renal biopsy. Among those 110 subjects, 73 (66.4%) had DKD; 20 (18.2 %) had NDKD; and 17 (15.4 %) had mixed kidney disease. Subjects with NDKD as compared with DKD had shorter duration of diabetes ($p<0.001$), absence of retinopathy ($p<0.001$) and absence of neuropathy ($p<0.001$). Logistic regression revealed that only presence of retinopathy and duration of diabetes were statistically significant to predict histopathological diagnosis of DKD. 30% of DKD did not have retinopathy, thereby limiting the utility of the same as a discriminator. Use of traditional indicators of biopsy would have indicated a need for renal biopsy in 87.2% of subjects, though 64.5% of the subjects had DKD, who would not have benefitted from biopsy.

Conclusion: NDKD and mixed kidney disease in T2DM with renal involvement are very common and traditionally used parameters to select biopsies are of limited value in clinical decision making.

Paper 3. 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 4. 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 5. 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 6. 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 7. 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 8. Yasmin, Masuma & Mukhopadhyay, Pradip & Ghosh, Sujoy. (2022). Model of care for Type 1 diabetes in India: Integrated approach for its incorporation in future national health care policy. The Lancet Regional Health - Southeast Asia. 3. 10.1016/j.lansea.2022.05.003.

Children and adolescents living with Type 1 Diabetes (T1DM) in India face multitude of challenges including lack of free supply of insulin, syringes, glucose measuring devices and strips, lack of structured diabetes education and counselling, and inadequately trained health care professionals. Multiple daily injections of insulin, self-monitoring of blood glucose, prevention of acute and chronic complications, structured diabetes education, psychosocial support, and safe disposal of sharps are essential components in the management of T1DM. Absence or disruption of standard care affects the physical and mental well-being of these children.

T1DM affects approximately million children and adolescents worldwide in the age group of 0-19 years, with 149,500 new cases being diagnosed every year. Data from International Diabetes Federation (IDF) Diabetes Atlas 2021 indicates that India has the world's highest number of children and adolescents suffering from T1DM.2 But in the absence of a nationwide T1DM registry, it is difficult to estimate exact numbers.
Government of India took initiative to launch the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) in the year 2008. This program is adult-centric with no initiatives to address juvenile non-communicable diseases (NCD).3 A few non-government organizations and pharmaceutical companies offer some support for T1DM in India.

However, these are all isolated piece meal initiatives. A recent study conducted in a tertiary health care facility in West Bengal, India found that mean glycated hemoglobin (HbA1c) level was 9.1± 2.36.

A structured national health care policy is the need of the hour. This could be part of a bigger overarching health care program such as juvenile NCD program.
Extensive literature search revealed that in developing countries, there is no structured health program for T1DM which is implementable, deliverable, replicable, scalable and pharmaco-economically viable.
We have embarked upon implementing a pilot model project for the management of T1DM in selected districts of West Bengal. This is a project-in-innovation, wherein a chronic care model is being developed for providing comprehensive health care for T1DM. The program is being implemented initially in five selected districts of West Bengal. Once the services get established successfully at these health facilities, the program will be scaled up to cover the remaining 23 health districts of West Bengal and later the whole country could possibly benefit from this model if proven to be beneficial and scalable.

The program focuses on providing comprehensive health care services for these children by utilizing the existing health care delivery system and piggy backs on the NPCDCS program. Comprehensive health care services at out-patient department (OPD) basis including detection, management of disease and complications, appropriate referral, and rehabilitation, counseling services, building registry of T1DM patients, training human resources, and capacity building at the community level are important components of the program.
Existing NCD clinics of each district hospital has been upgraded to T1DMclinic once a week after initial inspection and careful supervision. Existing identified human resources of each district hospital have been trained to provide comprehensive health care for T1DM. Each district hospital has been tagged with a medical college in the state for providing on-site training and hand-holding initially for six months. Children and adolescents with

T1DM receive effective treatment at these clinics along with free provision of insulin, glucose measuring devices and strips, routine anthropometric examination, required laboratory investigations, monthly follow up care services, emergency care services and timely referral to tertiary health care facility when necessary. Structured diabetes education is being provided to the children and their caregivers in the form of counselling
services at OPD basis by trained nursing staff, distribution of T1DM education booklets and quarterly educational camps. Children and adolescents with T1DM and their caregivers are trained for self-management, self-monitoring of blood glucose, insulin dose adjustment, sick day rules, nutrition and exercise, and awareness regarding complications. Counseling is the cornerstone for effective management of T1DM because proper selfcare ensures good glycemic control and psychological well-being. Children and their caregivers also have access to telephonic contact with trained program coordinator for emergency management. Web-based application has been developed where every treatment detail is recorded and updated in the form of initial, monthly and annual visit formats.
Through this program, long term sustainability of the interventions may be ensuredand mayimprove survival and quality of life of children and adolescents suffering from T1DM, bringing relief to a large section of the community across all classes irrespective of their
financial status.We are hopeful that in the long run juvenile NCD program will be launched in India based on our model of care for T1DM.

Paper 9. 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 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.