15. Danske Kongres i Klinisk Biokemi (DSKB)
Abstractbog

01 - Testosterone therapy increases the anticoagulant potential in men with opioid-induced hypogonadism: a randomized, placebo-controlled study

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Introduction: Hypogonadism is prevalent during opioid treatment and low testosterone concentrations are associated with cardiovascular disease. The effect of testosterone replacement therapy (TRT) on the coagulation system in men with hypogonadism is not clarified. We investigate effects of TRT on the tissue factor (TF) and contact activation pathways of coagulation in opioid treated men.
Materials and methods: Double-blinded, placebo-controlled study in 37 men with total testosterone < 12 nmol/l randomized to 24 weeks of testosterone injections (n = 17) or placebo (n = 20). Variables of the coagulation system were analysed at baseline and after 24 weeks. Measurements included the TF pathway (endogenous thrombin potential (ETP), peak thrombin), the contact activation pathway (endogenous kallikrein potential (EKP), peak kallikrein), coagulation factors (FVII, FX, prothrombin, FXII), and inhibitors (tissue factor pathway inhibitor (TFPI), protein C, protein S, antithrombin, C1 esterase inhibitor (C1inh)). Between-group differences at 24 weeks were determined with analysis of covariance. Within-group changes in TRT and placebo were analysed with paired t-test.
Results: Between-group differences at 24 weeks were observed for ETP ($p = 0.036$), FVII ($p = 0.044$), FX ($p = 0.015$), prothrombin ($p = 0.003$), protein C ($p = 0.004$), and protein S ($p = 0.038$). Within the TRT group, ETP, peak thrombin, FVII, FX, prothrombin, TFPI, protein C, FXII, and C1inh decreased and protein S increased (all $p < 0.05$). Within the placebo group, coagulation outcomes were unchanged.
Conclusion: TRT affects the coagulation system in an anticoagulant direction through suppressed TF pathway in men with opioid-induced hypogonadism.

02 - Validation of neuropsychiatric therapeutic intervals based on retrospective data from the laboratory information system

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Introduction
In clinical psychiatry, therapeutic drug monitoring is a tool to monitor pharmacological treatment. Therapeutic reference ranges and dose-effect relation are the main requirements for this drug titration tool. Updating these ranges is difficult and there are no standardised method for calculation and clinical qualification.

Materials and Methods
We have developed a model for selecting and validating routine laboratory data, hereby facilitating fast and automated calculation of therapeutic ranges. The model incorporates inclusion and exclusion parameters based on the frequency and time between sequential measurements from the same patient. The algorithm was applied on retrospective datasets from commonly prescribed antidepressiva and antipsychotic drugs, analysed at Aarhus University Hospital, Denmark. The calculated 10-90% percentiles were compared to published intervals.

Results
The therapeutic intervals can be divided into three groups: a) confirmation of existing intervals; b) minor adjustments needed; and c) potentially intervals to re-evaluation. Olanzapine (from 25-150 nmol/L to 35-250 nmol/L) and Sertraline (from 25-150 nmol/L to 30-200 nmol/L) are candidates for reconsideration of the upper limit. For Clomipramine, Paliperidone and Clozapine, the results confirm the existing intervals, and for Quetiapine, Ziprasidone and Venlafaxine, the results show the need of minor adjustments.

Conclusion
We designed a model and applied it to an algorithm capable of clustering and purifying the enormous information gathered from the Laboratory Information Management System (LIMS). This is the first step to make these data accessible and applicable for calculating better therapeutic reference ranges. The next step is the qualification of the found intervals together with clinicians.

03 - Cystatin C og Kreatinin i tidlig graviditet og forekomsten af autoimmun hypothyroidisme

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Baggrund:
De fysiologiske ændringer under en graviditet påvirker nyrefunktionen og thyroidea funktionen og niveauet af relaterede biokemiske analyser. En sammenhæng mellem niveauet af Cystatin C (CysC) og Kreatinin og thyroidea funktionen er fremhævet hos ikke-gravide, men sammenhængen er uafklaret hos gravide.
Metode:
Retrospektivt kohortestudie i Region Nordjylland (2011-2015), hvor der i median graviditetsuge 10 er målt thyroidea funktionsparametre og thyroidea autoantistoffer (Advia Centaur XPT, Siemens Healthineers) i overskydende serumprøver. I konsekutivt udvalgte prøver (n = 1,112) blev der målt CysC og Kreatinin (Atellica CH 930, Siemens Healthineers), og data blev koblet til nationale registre mhp. at a) etablere graviditetsspecifikke referenceintervaller for CysC og Kreatinin og b) evaluere forekomsten af maternel autoimmun hypothyroidisme (TSH over øvre metode og graviditetsuge-specifikke referenceintervalsgrænse samt thyroidea autoantistof positiv) ift. percentil-niveauer af CysC og Kreatinin.
Resultater:
De etablerede referenceintervaller (2,5-97,5 percentil) var afhængig af graviditetsugen og var for CysC (uge 4-8; 9-11; 12-15): 0,58-0,92 mg/L; 0,54-0,91 mg/L; 0,52-0,86 mg/L, og for Kreatinin: 46,9-73,0 µmol/L; 42,0-68,4 µmol/L; 38,8-66,4 µmol/L. Forekomsten af autoimmun hypothyroidisme i tidlig graviditet varierede med niveauet af CysC og Kreatinin (<25. percentil; 25.-75. percentil; > 75. percentil) og var for Cys C: 1,7%; 3,8%; 7,4% og for Kreatinin: 2,5%; 4,1%; 7,1%.
Konklusion:
Referenceintervaller for CysC og Kreatinin var dynamiske i tidlig graviditet med lavere niveauer for stigende graviditetsuge. Stigende niveauer af CysC og Kreatinin var associeret med en øget forekomst af autoimmun hypothyroidisme i tidlig graviditet. Resultaterne fører til overvejelser om den underliggende årsagsmekanisme for sammenhæng mellem thyroideasygdom og CysC hos gravide og ikke-gravide.

04 - Hvor mange patienter er svære at tage blodprøver på?

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Introduktion:
At afdække patienters subjektive opfattelse af, om de er svære at foretage blodprøvetagning på, og at sammenholde dette med prøvetagernes oplevelse af prøvetagningen.

Materialer og metoder:
Ovenstående blev afdækket ved hjælp af et spørgeskema, som . Spørgeskemaet blev lagt i vores ambulatorie tre dage i december 2022. Det bestod af følgende tre spørgsmål:

1. Spørg før prøvetagningen patienten om, hvorvidt han/hun plejer at være svær at tage blodprøver på
2. Angiv efter prøvetagning, om du synes, at patienten var svær at stikke
3. Hvis ja til spørgsmål 2, skal følgende angives:

- Lykkes efter 1 forsøg
- Lykkes efter 2 forsøg
- Måtte tilkalde hjælp fra kollega. Hvis der blev tilkaldt hjælp: Lykkedes det for din kollega?

Resultater:
235 patienter (30% af alle patienter, der var til prøvetagning i løbet af de tre dage) og 11 forskellige prøvetagere indgik i denne undersøgelse.
I alt 67 (29%) af patienterne angav, at de var svære at tage blodprøver på.
Vurderet af prøvetagerne var det kun 39% af de 67 patienter, der angav, at de var svære at tage blodprøver på, som reelt var svære (= ikke lykkedes i første forsøg).
Prøvetagere med kortest anciennitet (< 1 år) er dem, som oftest bruger flere forsøg og oftest må tilkalde hjælp fra kollega.

Konklusion:
Denne undersøgelse viser, at over halvdelen (61%) af de patienter, der vurderer, at de er svære at tage blodprøver på, ikke er det.
Resultaterne kan måske anvendes som et pædagogisk værktøj i forbindelse med træning i blodprøvetagning.

05 - Måling af B-Trombocytter i $MgSO_4$- og citrat-blod.

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Introduktion

Visse patienter præsenterer med trombocyt-agglutinationer, hvilket leder til ikke-revisende måling af B-Trombocytter. Agglutination er anset for at være forårsaget af EDTA, der anvendes som anti-koagulans. Der findes prøvetagningsglas med alternative anti-koagulanser til EDTA, herunder citrat og $MgSO_4$. Trombocytbestemmelse i citrat- og $MgSO_4$-glas sammenlignes med K_2-EDTA-glas på Abbotts Alinity hq og Siemens Advia 2120i.

Materialer og metoder

EDTA-, citrat- og $MgSO_4$-blod fra 40 tilfældigt udvalgte ambulante patienter er indsamlet på Regionshospitalet Gødstrup. Analysering af prøverne er påbegyndt inden for en time efter prøvetagning. Prøverne er færdiganalyseret inden for 4 timer.

Resultater

Ved bestemmelse af B-Trombocytter i $MgSO_4$-blod ses 29 % lavere værdier end ved EDTA-blod på Alinity Hq. Analysering af citrat-blod viser tilsvarende 30 % lavere antal trombocytter.
Ved bestemmelse af B-Trombocytter på Advia ses også lavere antal, hhv. 17% lavere for $MgSO_4$-blod og 19 % lavere for citrat-blod.

Konklusion

Analysering af blodprøver fra tilfældige ambulante patienter kan ikke anbefales at få målt B-Trombocytter i $MgSO_4$- eller citrat-blod, da analyseresultaterne vil være markant lavere på både Alinity hq og Advia 2120i. Dog er det uklart, hvilken effekt $MgSO_4$ eller citrat vil have på blod, der udviser trombcytagglutination ved måling i EDTA-blod.

06 - Pediatric reference interval for plasma calprotectin

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Introduction
Plasma calprotectin is a promising new biomarker of inflammatory activity and has been found to correlate well with clinical and endoscopic activity in children and adolescents with inflammatory bowel disease. A pediatric reference interval for plasma calprotectin has not been established. Pre-analytical studies have shown excellent precision and stability for the Phadia 250 EliATM Calprotectin flouroenzyme-immunoassay, however, sensitivity to hemolysis was demonstrated. Hemolysis is a common pre-analytical issue, especially in children.
Materials and methods
Based on an automated search algorithm in the laboratory information system LABKA, we identified blood samples from apparently healthy children who were referred by their general practitioner for measurement of hemoglobin and C-reactive protein. We excluded samples if additional blood sampling was requisitioned within 2 months before or after the index sample, or if hemoglobin or C-reactive protein levels were outside of reference intervals, and any samples with a hemolysis above 25 mg/mL.
Results
We identified 151 blood samples, of which 2 were discarded due to hemolysis. No outliers were identified. We established the following reference intervals according to CLSI C28-A3 using non-parametric statistics: 0– 18 years: 16-266 ng/mL. Assessment ad modum Lahti lead to partitioning into groups of 0-10 years (n=65): 20-287 ng/mL and 11-18 years (n=84): 13-218 ng/mL.
Conclusion
We established age-specific pediatric reference intervals for plasma calprotectin using the Phadia 250 EliATM Calprotectin flouroenzyme-immunoassay in a Danish cohort. Our results will be useful for further utilization of calprotectin as an alternative marker of inflammation in children and adolescents with inflammatory disorders.

07 - No detectable coagulation activation after vitamin K (MK-7) supplementation in patients on dialysis with functional vitamin K deficiency: a one-year randomized, placebo-controlled study

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Introduction: Patients on dialysis treatment have poor functional vitamin K status, and this may increase the risk of vascular calcification. Vitamin K supplementation may therefore be relevant in patients on dialysis, but the procoagulant effects have not been studied. We evaluated effects of high-dose menaquinone-7 (MK-7) supplementation on biomarkers of coagulation in patients on dialysis.

Materials and Methods: Double-blinded, placebo-controlled study in 123 patients on dialysis randomized to 52 weeks of vitamin K (MK-7, 360 µg/daily, n=61) or placebo (n=62). Measurements at baseline and after 52 weeks of intervention included thrombin generation (endogenous thrombin potential (ETP), peak thrombin concentration, time to peak, and lag time), clot activities of vitamin K-dependent coagulation factors (F) II, VII, IX, and X, prothrombin fragment 1+2 (F1+2), and proteins induced by vitamin K absence II (PIVKA-II). Between-group differences (vitamin K vs. placebo) at 52 weeks were determined with an analysis of covariance. Within-group changes in vitamin K and placebo groups were analyzed with a paired t-test.

Results: A between-group difference at 52 weeks was observed for PIVKA-II ($p<0.001$). PIVKA-II decreased significantly from baseline to 52 weeks in the vitamin K group, but not in the placebo group. We observed no other between-group differences or within-group changes, except for FVII clot activity which was reduced in the placebo group ($p=0.04$).

Conclusion: One year of high-dose vitamin K supplementation in patients on dialysis has no detectable effects on biomarkers of coagulation activation and clot activities of vitamin K-dependent coagulation factors, indicating no procoagulant effects of this treatment.

08 - Kvalitetskrav til Analyser som bruges i Algoritmer

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Introduktion:
Algoritmer kan være sensitive over for variation i input-variable og succesfuld implementering af klinisk machine learning afhænger derfor i høj grad af tilstrækkelig analysekvalitet.
For simple algoritmer, kan samlet variation som følge af analysevariation beregnes via variansregneregler, men for mere komplekse algoritmer er det ikke muligt benytte den metode. Man kan i stedet benytte simulationsforsøg. Vi demonstrerer simulations-processen ved hjælp af en klinisk algoritme – Model of End Stage Liver Disease (MELD), som benyttes til at risikostratificere cirrosepatienter.
Materialer og metoder:
Vi ekstraherede 6 måneders produktion af MELD-scorer (1207 MELD-scorer) og underliggende analyseresultater fra laboratoriedatabasen på Vejle Sygehus. Vi fandt værdier for "ønskværdig" analytisk variation i litteraturen og simulerede denne variation oven på det eksisterende dataset for hver input variabel for sig og på alle tre variable sammen. Hver simulation blev gentaget 1000 gange. Herefter beregnede vi andelen af prøver, som blev re-klassificeret til en anden risikokategori.
Resultater:
Re-klassifikationsraten var 1,37% ved simulation af variation på Kreatinin (CV% 2,2), 2,5% ved simulation på bilirubin (CV% 10,5) og 7,97% ved simulation på INR (CV% 4,5). Ved simulation på alle tre variable samtidig var re-klassifikationsraten 9,39%.
Konklusion:
I den undersøgte population var MELD-score meget sensitiv for analytisk variation af INR, imens variation af bilirubin- og kreatinin-resultater var af mindre betydning.
Dette eksempel demonstrerer, at selv simple algoritmer kan reagere uforudsigeligt på ændringer i analytisk variation og viser, hvordan simulation kan benyttes til at teste kvalitetskrav og undersøge, hvor følsomme algoritmerne er for de enkelte inputvariable. Dette kan lede til skærpede analysekvalitetskrav.

11 - Validation of an ELISA using a new monoclonal antibody specific for the C-terminal fibrinogen γ' chain: effects of obesity surgery

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Introduction: Fibrinogen γ' is a naturally occurring splice variant with a 20 amino acid extension of the fibrinogen γ chain. Animal studies link variations of fibrinogen with obesity, but it is unknown how fibrinogen γ' is associated with obesity in humans. We have developed and validated an enzyme-linked immunosorbent assay (ELISA) for quantification of fibrinogen γ' in human plasma and analyzed fibrinogen γ' before and after obesity surgery.

Materials and Methods: We generated C-terminal fibrinogen γ' specific mouse monoclonal antibodies for ELISA development. Validation included measures of accuracy, sensitivity, and precision. Fibrinogen γ' and total fibrinogen were measured in 60 individuals before and six months after obesity surgery, 19 normal weight controls, and 120 blood donors.

Results: Highly specific fibrinogen γ' monoclonal antibodies were produced and successfully used in the ELISA. Recovery was 88 % and limit of detection and quantification were 0.003 mg/mL and 0.014 mg/mL, respectively. Coefficients of variation were 3% for repeatability and 7% for within-laboratory variation. The fibrinogen γ' reference interval was 0.25-0.80 mg/mL. Fibrinogen γ' concentrations were reduced after obesity surgery and were lower in normal weight individuals than in individuals with obesity. The fibrinogen γ'/total fibrinogen ratio was unchanged after surgery, but was lower in normal weight individuals.

Conclusion: We developed a precise and sensitive ELISA for fibrinogen γ'. Levels of fibrinogen γ', but not the fibrinogen γ'/fibrinogen ratio, were reduced six months after obesity surgery. Absolute and relative levels of fibrinogen γ' were both increased in obesity compared with normal weight.

12 - A new enzyme-linked immunosorbent assay to quantify sialylated fibrinogen in plasma

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Introduction: Stroke is a major cause of death globally, and diabetes patients are at higher risk of developing a stroke than non-diabetes individuals. The reason for this is unclear, however, plasma fibrinogen seems to be involved due to its central role in clot formation and inflammation. Fibrinogen can be glycated or glycosylated in the presence of high blood glucose levels, which is often present in diabetes patients. Glycated fibrinogen modulates clot structure, making it more resistant to lysis, but only little is known about the effects of glycosylation on fibrin clots and the risk of stroke.

Materials & Methods: We are developing an enzyme linked immunosorbent assay (ELISA) for quantification of glycosylated (sialylated) fibrinogen in human plasma.
In brief, a microtiter plate is coated with a polyclonal rabbit anti-human fibrinogen antibodies and the plate is incubated with citrate plasma. Sialic acids on fibrinogen are detected by biotinylated Sambucus Nigra lectin (SNL) and quantified using HRP-conjugated streptavidin and peroxidase enzyme substrate. The plate is read at 450 nm and the color intensity is proportional to the amount of sialic acids on fibrinogen. To eliminate the risk of unspecific binding of SNL, neuraminidase (which cleaves sialic acids) serves as a blank control. The assay is calibrated against a citrate plasma pool from healthy individuals, and the level of sialic acids is expressed relative to the fibrinogen concentration.

Results: Next, the method will be validated and applied on samples from diabetes patients with stroke, diabetes patients without stroke, and healthy controls.

14 - Metabolism of 25-hydroxy-vitamin D in human macrophages is highly dependent on macrophage polarization

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Introduction: Macrophages synthesize active vitamin D (1,25-dihydroxy-vitamin D) and express the vitamin D receptor in the nucleus, however, vitamin D metabolism in relation to macrophage polarization and function is not well understood. Material and Methods: We studied monocyte-derived macrophages (MDMs) from human buffy coats polarized into M0, M1 (LPS+IFNγ), M2a (IL4+IL13) and M2c (IL10) macrophage subtypes stimulated with 25-hydroxy-vitamin D (1,000 and 10,000 nanomolar). We measured vitamin D metabolites (25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, 24,25-dihydroxy-vitamin D and 3-epi-25-hydroxy-vitamin D) in cell media with liquid chromatography-mass spectrometry-mass spectrometry. The mRNA expression (CYP27B1, CYP24A1 and CYP24A1-SV) was measured with qPCR. Results: We found that reparative MDMs (M2a) had significantly more 1,25-dihydroxy-vitamin D compared to the other MDMs (M0, M1 and M2c). All MDMs were able to produce 3-epi-25-hydroxy-vitamin D, but this pathway was almost completely attenuated in inflammatory M1 MDMs. All MDM subtypes degraded vitamin D through the 24-hydroxylase pathway, although M1 MDMs mainly expressed an inactive splice variant of CYP24A1 coding the degrading enzyme. Conclusion: This study shows that vitamin D metabolism is highly dependent on macrophage polarization, and that the C3-epimerase pathway for vitamin D is active in macrophages.

16 - Forbrug af HbA1c analysen i almen praksis: nærmer vi os befolkningsscreening?

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Introduktion: Der synes ikke at være en samfundsmæssig gevinst ved systematisk befolkningsscreening for diabetes. Til trods herfor fornemmer vi, at vi er på vej derhen pga. et stadigt stigende antal HbA1c målinger, især fra almen praksis. For at kvantificere dette, har vi gennemgået vores HbA1c produktion fra de sidste 4 år.
Materialer og metoder: Vi lavede et udtræk af alle HbA1c målinger rekvireret fra almen praksis analyseret på vores afdeling i perioden januar 2019 – november 2022. Rekvisitioner, hvor der ikke blev afgivet et numerisk svar, blev ekskluderet.
Resultater: Størstedelen af patienterne var kvinder (55,3%) med en median alder på 53,6 år (IQR 34,4 – 69, 0). Median alder for mænd var 56,0 år (IQR 40,0 – 69,0). Gennemsnitlige HbA1c i datasættet var 38 mmol/mol (IQR 35 – 43 mmol/mol). Hovedparten (69,4%) af HbA1c resultater var < 42 mmol/mol, mens 15,5% var > 48 mmol/mol. Der var overordnet 550.727 HbA1c resultater fordelt på 184.065 patienter, sv.t. 2,98 målinger pr. patient (range 1 – 33). Gentagne målinger blev i 6,7% af tilfældene udført indenfor 8 uger, mens 11,0% blev gentaget indenfor 12 uger. Antallet af HbA1c resultater pr. rekvirent varierede fra 103 – 24.034 (median 5.517). Rekvirenterne havde samlet 345.494 sikrede patienter, hvoraf 53,6% fik analyseret HbA1c i perioden.
Konklusion: Over halvdelen af de sikrede patienter fra almen praksis fra vores optageområde fik målt HbA1c i løbet af knapt 4 år. Langt størstedelen af resultaterne var < 42 mmol/mol. Vores gennemgang tyder på, at vi nærmer os en befolkningsscreening for diabetes.

17 - The RefIT software provides fast and automated verification of reference and therapeutic ranges based on large laboratory datasets

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Introduction : Therapeutic drug monitoring (TDM) is a clinical tool, where the concentration of a therapeutic drug in a biological matrix, is used to optimize and individualize the treatment of a patient. One of the main requirements is the availability of a therapeutic reference range to guide the therapy. Defining and validating these ranges are difficult, as there are no consensus method available for calculation them. Furthermore, as analytical methods and treatment regimes may change over time, published reference ranges should continuously be verified and updated.
Materials and Methods : We designed, programmed and validated the RefIT software (– Reference Interval Tool –) using vb.net.
Results : The RefIT software provides automatic cleanup and selection of data from large laboratory datasets. Validation and selection of patient results can be achieved using different data models, as well as sex and age. In addition, the software provides multiple functions for calculating and visualization of reference ranges. RefIT takes input in the form of excel files, and export calculated ranges in the same format. All graphs can be exported as image files for further use in presentations.
Conclusion : The RefIT software provides a fast and convenient way of calculating reference and therapeutic ranges based on big-data. RefIT version 1.0 is standalone software that runs on Windows, is freeware, and can be downloaded from github (https://github.com/JensLarsen/RefIT/releases/tag/V1.0). Documentation is included in the zip file along with a sampleset for testing.

18 - Er manuel validering af maskinelle differentialtællinger med flag overflødig?

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Manuel differentialtælling udføres ofte som validering af en maskinel differentialtælling, der har udløst alarm ("flag") på udstyret, f.eks. pga. mistanke om blaster. Manuelle differentialtællinger er tidskrævende, og mange laboratorier kan kun tilbyde den i dagtid på hverdage. Vi ønskede derfor retrospektivt at opgøre den kliniske gevinst ved disse manuelle valideringer, særligt betydningen ift. at erkende alvorlig hæmatologisk sygdom.

Vi identificerede alle rekvirerede maskinelle differentialtællinger på Regionshospitalet Horsens i perioden okt. 2019 – sep. 2021 analyseret på Sysmex XN9000 samt tilhørende manuelle differentialtællinger udført vha. CellaVision DM. Vi sammenlignede automatiserede og manuelle tællinger af de enkelte leukocyttyper og indhentede detaljerede kliniske oplysninger om patienter med fund af blaster.

Ud af 10.116 manuelle differentialtællinger blev den maskinelle tælling blot bekræftet i 6.647 tilfælde. I 1.346 tilfælde blev tællingen modificeret, men der var stadig god overensstemmelse mellem manuelle og maskinelle celletal for modne celler, herunder neutrofile granulocytter i lavt niveau. Blaster blev rapporteret i 189 af de modificerede tællinger og var hyppigst et forbigående/tilfældigt fund. I 12 tilfælde blev der efterfølgende erkendt ny hæmatologisk sygdom, men fundet af blaster havde i ingen tilfælde afgørende betydning for henvisning til hæmatologisk afdeling.

Samlet set konkluderer vi, at manuel eftertælling af maskinelle differentialtællinger med "flag" ikke havde væsentlig klinisk værdi. Fund af blaster i disse prøver var hyppigst tilfældige og forbigående fund, og i ingen tilfælde var de afgørende ift. at diagnosticere alvorlig, hæmatologisk sygdom. Man bør derfor overveje, om brugen af ressourcer på disse eftertællinger er hensigtsmæssig i et moderne sundhedsvæsen.

21 - Congenital hypodysfibrinogenaemia due to γ326Cys->Tyr mutation: Third ever described case associated with recurrent venous thrombosis induced by COVID vaccine.

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Introduction:
Congenital fibrinogen disorders (CFDs) are a heterogenous group of fibrinogen defects including afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia and hypo-dysfibrinogenemia. Due to the variation of the clinical phenotype of CFD, diagnosis and management of patients can be challenging. We present a case of hypodysfibrinogenemia with recurrent provoked deep venous thrombosis (DVT).

Methods and results:
The proband, a 33-year-old female of Turkish descent had her first provoked DVT at the age of 20 during her first pregnancy. Thrombophilia investigation was normal except decreased levels of fibrinogen both functional and immunological method and prolonged thrombin time indicating hypo-dysfibrinogenemia. In 2021 she received the Pfizer-BioNTech Covid-19 vaccine, where she shortly after developed her 2nd DVT. To elaborate the genotype-phenotype associations fibrin structure assays whole-exome sequencing (WES) were performed. The fibrin structure assays showed polymerization defect, but otherwise normal. WES identified the γ326Cys->Tyr mutation combined with single nucleotid polymorphisms (SNP)s rs2070011, rs2070018 in FGA and in rs1049636 in FGG . The patient was subsequently put on lifelong rivaroxaban treatment.

Conclusion:
We present the third ever described case with γ326Cys->Tyr mutation together with SNPs, in FGG and FGA, that is associated with hypodysfibrinogenemia and DVT. All other cases with same mutation had also thrombosis. The mechanism why these mutations induce thrombosis is still unknown. We speculate that the SNP, rs1049636 in FGG might contribute to the thrombogenic phenotype, which previously has been reported to be related to VTE risk. This is the first study focusing on the possible impact of SNPs on the clinical phenotype of hypodysfibrinogenemia.

22 - Holdbarhed af sIgE-analyser: Præanalytisk håndtering

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Introduktion
Immunglobuliner betragtes som stabile molekyler, men holdbarheden af allergen-specifik immunglobulin E (sIgE) er ikke systematisk undersøgt. Vi ønskede med udgangspunkt i laboratoriets rutineprocedurer at undersøge forskellige præanalytiske faktorers betydning for holdbarheden af sIgE.

Materialer og Metoder
Prøvemateriale fra frivillige med kendte allergier eller rutineprøver fra patienter blev anvendt. sIgE i serum blev målt med ImmunoCAP-assays på et Phadia1000 instrument (Thermo Fisher Scientific), enten i prøvetagningsrør (silica med gel) eller i sekundærrør (plast uden tilsætning). Målte sIgE-værdier blev sammenlignet med sIgE-niveauet i referenceprøver (centrifugeret <90 min. og analyseret <3 timer efter prøvetagning) og vurderet ift. krav til bias og TE. Følgende præanalytiske forhold blev undersøgt: Udskudt centrifugering, opbevaringstid ved 5 ºC, opbevaringstid- og -måde ved –20 ºC samt gentagne fryse-tø cykler.

Resultater
- sIgE er holdbar i primærrør (serum på gel) i 48 timer inden centrifugering
- sIgE er holdbar i serum i 10 dage på køl
- Gelmaterialet påvirker ikke sIgE-måling ved nedfrysning i primærrør i 7 dage
- Gentagne nedfrysninger eller frysning i 4-8 uger medfører større variation i sIgE-resultater

Konklusion
Vores studie bekræfter, at sIgE er stabilt. Vores hidtil anvendte holdbarhedsangivelse (centrifugering af primærrør inden 10 timer og holdbarhed på køl i 7 dage) kan udvides, hvorved kassering af ucentrifugerede indsendte prøver kan undgås. Allergiprøver nedfryses rutinemæssigt mhp. mulighed for efterbestilling i 4 uger. Dette giver en øget variation på analyseresultaterne, som dog klinisk, pga. manglende direkte sammenhæng mellem sIgE-niveau og graden af allergisk reaktion, vurderes uden betydning. En undersøgelse af holdbarhed ved stuetemperatur vil være relevant.

24 - Triglycerides and cholesterol in apolipoprotein B lipoproteins and risk of clinically diagnosed non-alcoholic fatty liver disease and myocardial infarction in 25,428 individuals from the Copenhagen General Population Study

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Background and Aims: Cardiovascular disease is the leading cause of death in individuals with non-alcoholic fatty liver disease, and we speculate that a potential mechanism may evolve around apolipoprotein B (apoB) containing lipoproteins, and in particular very low-density lipoproteins (VLDL), as they carry triglycerides and cholesterol in the same particle. We hypothesized that VLDL triglycerides content associate with risk of non-alcoholic fatty liver disease, while VLDL cholesterol content associate with risk of cardiovascular disease.
Material and methods: Study of the general population in the Copenhagen area using high throughput nuclear magnetic resonance spectrometry concentrations of triglycerides and cholesterol in VLDL, intermediate-density lipoprotein, and low-density lipoprotein (LDL) as well as the concentration of apoB containing lipoprotein were determined.
Results: Risks of non-alcoholic fatty liver disease were 1.61 (95% confidence intervals: 1.25-2.06) and 1.41 (0.90-2.21) for individuals with VLDL triglycerides concentration >66th percentile, and VLDL cholesterol concentration respectively above and below the 66th percentile. Conversely, risks of myocardial infarction were 1.51 (1.36-1.67) and 1.42 (1.18-1.69) for VLDL cholesterol >66th percentile, and VLDL triglycerides respectively above and below the 66th percentile. Risk was 1.09 (0.90-1.33) for VLDL cholesterol ≤66th percentile and VLDL triglycerides concentrations >66th percentile.
Discussion and conclusions: Risk of clinically diagnosed non-alcoholic fatty liver disease increased with increasing concentration of triglycerides in VLDL, regardless of cholesterol level or lipoprotein concentration. Risk of myocardial infarction increased with increasing cholesterol and lipoprotein concentrations in all apoB containing lipoproteins.

27 - Antiphospholipid antibodies in pulmonary embolism treated with direct oral anticoagulants: Prevalence data from unselected consecutive patients

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Introduction
Direct oral anticoagulants (DOAC) are the first-choice treatment to prevent recurrence of venous thrombosis in patients with pulmonary embolism (PE); however, their effect in patients with antiphospholipid syndrome (APS) has been challenged. Our objective was to determine the prevalence of unselected patients presenting with PE, who meet the criteria for APS based on elevated anticardiolipin (aCL) and anti-β2-glycoprotien I (aβ2GPI) antibodies.

Materials and Methods
Consecutive patients with PE, primarily initiated with DOAC, were tested for aCL and aβ2GPI. If elevated, tests were repeated after 12 weeks for APS diagnosis. Lab results and patient characteristics were retrospectively collected from a laboratory information system and electronic patient journal entries over a 2-year period.

Results
The prevalence of APS based on consistently elevated aCL or aβ2GPI was 3.7% (10/267 patients). Three patients were double positive. In 11 out of 21 patients (52%) with initially elevated values, antibodies normalized after 12 weeks. Patient characteristics were largely similar in those with and without APS, but patients with APS tended to be older and more likely to receive antithrombotic treatment at the time of PE.

Conclusion
We found a relatively low prevalence of APS based on aCL or aβ2GPI. The high rate of normalized antibodies after 12 weeks reaffirms the need for repeated tests for APS diagnosis. Older patients more frequently met criteria for APS. Determining the effectiveness of DOAC in non-triple positive APS following VTE is important to further determine the feasibility of unselected tests in patients with PE.

28 - Differentieltælling ved brug af flow-cytometri: en ny strategi

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Introduktion: Automatiseret (maskinel) differentialtælling er standard-analysen i de fleste laboratorier, men når den udløser alarm ("flag"), bliver leukocytterne yderligere evalueret med hjælp af morfologi på et udstryg (manuel differentialtælling). Ikke desto mindre er den manuelle differentialtælling en tidskrævende og subjektiv analyse, med en relativ stor sandsynlighed for fejl og misklassificering af de forskellige typer af leukocytter, idet man kun undersøger omkring 200 celler. Derfor vil dette studie undersøge hvorvidt differentialtælling ved brug af flowcytometri (FlowDiff) potentielt kan diagnosticere maligne hæmatologiske tilstande både hurtigere og mere sikkert, og kan derfor være med til optimere de relevante patientforløb.

Materialer og metoder: Vi vil bruge et panel bestående af 8 farver (fluorokromer) og i alt 11 antistoffer, som er inspireret af det IVDR-godkendte Euroflow consortium. Det primære formål er at udføre metodesammenligning og evaluere overensstemmelsen af FlowDiff med både maskinel-diff og manuel-diff, men der vil også vurderes forskellige aspekter af metoden (præcision, linearitet, sensitivitet-LoD/LoQ).

Resultater: I skrivende stund har vi evalueret panelet i en Gallios flowcytometer (Beckman Coulter) og kunnet identificere de følgende 8 cellepopulationer: neutrofilocytter, eosinofilocyter, basofilocytter, umodne granulocytter, monocytter, lymfocytter, plasma celler, og blaster. FlowDiff viser en god overensstemmelse med Sysmex for de 6 leukocyt-populationer, som Sysmex inkluderer i dens diff-tælling. Der insdamles fortsat data med henblik på sammenligning af FlowDiff og både Sysmex og manuel-diff, som vil præsenteres på konferencen.

Konklusion: Vi forventer at FlowDiff vil med fordel kunne bruges til differentialtælling og eventuelt optimere diagnostik hos patienter med en malign hæmatologisk sygdom.

29 - Mild traumatic brain injury – performance of new biomarker-assay for measuring GFAP and UCH-L1

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Introduction
Glial fibrillary acidic protein (GFAP) and Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) is a combinational biomarker (Abbott) for mild traumatic brain injury. It is not included in the guideline from the Scandinavian Neurotrauma Committee due to insufficient scientific investigation. The aim was therefore, to perform a preliminary investigation of the analytical performance.
Material and methods
Precision of GFAP and UCH-L1 was calculated from repeated measurements of quality controls, over a period of 5 days (n=30). Comparison of blood collection tubes, lithium heparin with gel (LI) and serum with gel (serum) were performed with measurements in duplicate on samples from healthy individuals (n=10).
Results
CV for the GFAP controls at levels between 25 ng/L and 30,683 ng/L were 2.5-4.0%. For UCH-L1, corresponding results were 3.1-3.7% for the levels 250 ng/L-15,029 ng/L. Range of GFAP for healthy individuals was 12.15-83.3 ng/L, with the highest relative difference 14% and 8% for duplicates on LI and serum respectively. Maximum relative difference between GFAP LI and serum was -11%. Corresponding results for UCH-L1 with the range of 49.75-166.65 ng/L were 67% for LI and 9% for serum. Maximum relative difference between LI and serum UCH-L1 was 39%.
Discussion and conclusion
The precision was satisfactory for both parameters at all three levels. Unfortunately, independent internal controls were not available. The relative difference on duplicate measurements for GFAP LI and serum were small, and LI and serum results seems to be comparable. For UCH-L1, serum seems to be noticeably more stable compared with LI.

30 - Falsk forhøjede elektrolyt- og laktatkoncentrationer på kapillærprøver fra børn analyseret på ABL – præanalytisk eller analytisk årsag?

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Introduktion

Kalium er en stramt reguleret parameter. På Aalborg Universitetshospital (AAUH) og Esbjerg Sygehus (ESB) er der ved flere tilfælde observeret meget høje kaliumkoncentrationer (>7 mmol/L) for kapillærprøver målt på både ABL800 og 90. Behandling ud fra fejlagtige resultater kan være fatalt. Problemstillingen er indberettet til Radiometer og Lægemiddelstyrelsen. Formålet med undersøgelserne var at afdække årsager til de sporadiske variationer.

Materialer og metoder

Forskellige undersøgelser er foretaget:

- Præanalytiske: Prøvetagning, prøvetager, varme/kolde fingre, hæmolyse, prøverør, opblanding af prøvemateriale, alder.
- Analytiske: Præcision. Metodesammenligning ved kalium >6,0 mmol/L prøvetaget i plastikkapillærrør, samt på raske voksne på ABL800 vs. ABL90 (AAUH)/Alinity (ESB).
- Patientrelaterede: sygdom, viskositet

Resultater

Forhøjede kalium-værdier var ofte ledsaget af forhøjet laktat og calcium, men normal natrium og klorid. Ved gentagen prøvetagning og analysering på anden ABL90 (AAUH) eller Alinity (ESB), blev der fundet normale værdier.

For kalium var præcision, samt metodesammenligning på raske voksne (n=5) acceptable. Problemerne blev observeret efter indførsel af plastikkapillærrør og sås hos børn (under 6 år), specielt hos de der var oprørte ifm. prøvetagningen. Børnene havde ofte RS-virus eller COVID. Anvendelse af håndsprit, samt prøvetagning i hhv. kolde og varme fingre viste ingen forskel.

Diskussion og konklusion

Afvigelserne tyder ikke på hæmolyse, da natrium og klorid er normale. Man kan mistænke interferens fra plastmaterialet i kapillærrørene, man har dog ikke set problemet i prøver fra voksne. Esbjerg har stoppet analysering af kalium på kapillærprøver og Aalborg har indført ekstraordinære procedurer ifm. prøvetagning og analysering. Afdelingerne samarbejder fortsat intensivt for at finde årsagen.

31 - The importance of combining both phenotypical, genetic and familial information in the diagnosis and management of dysfibrinogenemia

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Introduction

Congenital dysfibrinogenemia (CD) is caused by structural changes in fibrinogen that modify its function. The CDs, most often associated with bleeding disorders, encompass mutations in fibrinogen α-chain consisting of Gly17-Pro18-Arg19-Val20, known as knob A. However, the clinical picture associated with mutations at residue Arg19 varies including both bleeding, and/or thrombosis. We present a case with mutation (p.Arg19Gly) also known as the Fibrinogen Aarhus.

Methods and results

The proband, 45-year old woman with low fibrinogen level detected incidentally was asymptomatic without previous thrombosis or bleeding events. Her father had myocardial infarction at young age and her sons has tendency for nosebleeds. Diagnosis of the dysfibrinogenemia is based on discrepancy between decreased fibrinogen activity and normal fibrinogen antigen levels and is confirmed by genetic testing using two sequencing methods (targeted NGS and WES). Both identified a heterozygous mutation in FGA exon 2 (c. 112 G>A) (p.Arg19Gly) combined with single nucleotide polymorphism (SNPs) in FGA, FGB and FGG. The patient was informed about clinical events related the mutation and advised for family screening.

Conclusion

An accurate molecular characterization of Aα Arg19Gly dysfibrinogenemia is not sufficient to predict the clinical outcome, since this mutation is associated with a widely varied clinical outcome. Therefore, the family history is important. However management of asymptomatic patients with family history both thrombosis and bleeding as in present case, can be challenging for clinicians in a high-risk situation such as surgery. The impact of additional SNPs of fibrinogen on the phenotype of this mutation remains to be determined.

33 - The association between Urinary:Plasma Prostate Specific Antigen ratio and ISUP Score

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Introduction: Plasma prostate-specific antigen (PSA) has limited accuracy in early diagnosis and clinical decision-making in prostate cancer. This study aims to evaluate the usefulness of the urinary:plasma PSA ratio in the differentiation between benign prostate hyperplasia and prostate cancer.
Materials and Methods: This nested case-control study used urinary and plasma PSA results from 365 treatment naïve individuals, enrolled in the PerPros biobank (reference no.: S-20210085) between 2015 and 2021. Plasma and urinary samples were collected before the prostate biopsy. Biopsy tissue specimens were graded according to the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. A urinary:plasma PSA ratio <26 was considered low. Using multinomial logistic regression, relative risk ratios (RRR) for ISUP score with 95% confidence intervals (CI) comparing patients with high and low urinary:plasma PSA ratios were estimated.
Results: The study included 97 controls with benign prostate hyperplasia, 35 prostate-cancer patients with an ISUP score =1, and 233 with an ISUP score ≥2. Using controls as a reference group, a low urinary:plasma PSA ratio was not associated with ISUP score =1 (RRR 1.80, 95% CI 0.78-4.16) compared to a high ratio; however, a low ratio was associated with ISUP score ≥2 (RRR 6.30, 95% CI 3.34-11.86). The sensitivity for ISUP score ≥2 was 0.90 and the specificity 0.41, while the likelihood ratio positive was 1.52 and the likelihood ratio negative was 0.25.
Conclusion: The urinary:plasma PSA ratio may contribute to a better selection of patients for referral on suspicion of prostate cancer.

34 - Blodgas, samt syre-base parametre i glas- og plastikkapillærrør - et klinisk centralt studie

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Introduktion
Til bestemmelse af blodgas, samt syre-base parametre anvendes ofte kapillærrør til specielt de helt små patienter.
Hidtil har kapillærrør været lavet af glas, men er nu kun tilgængelig i plastik, hvilket potentielt kan påvirke holdbarheden af prøvematerialet og således den påkrævede turn-around-time for valide analysesvar.
Vi præsenterer et omfattende studie over blodgas og syre-base parametre målbare på ABL udstyr (Radiometer, Denmark) udført som et samarbejde mellem tre forskellige hospitalsenheder.

Materialer og metoder:
Metodesammenligning (N = 40) på 100 µl Clinitubes (glas) versus SafeClinitubes (plastik) er udført på ABL835 udstyr. SafePICO sprøjter er opblandet, to kapillærrør (glas/plast) er fyldt herfra, udluftet, forseglet og analyseret på skift.
I tillæg hertil er der udført holdbarhedsstudier (N = 15) på plastikkapillærrør med tre forskellige volumener (65 µl, 100 µl og 125 µl) til tiderne 10 minutter og 30 minutter. Ovenstående beskrevne procedure er anvendt, dog med lysbeskyttelse under opbevaring.

Resultater
Vores metodesammenligningsstudie mellem glas- og plastikkapillærrør viser klinisk ubetydelig divergens mellem de to materialetyper.
Holdbarhedsstudierne viser, at leverandørens grænse på 10 minutter kan udvides til 30 minutter for hovedparten af blodgas, samt syre-base parametrene.

Diskussion og konklusion
Der er et sikkerhedsmæssigt issue i at anvende plastik frem for glaskapillærrør, men påvirkning af fuldblodsprøvematerialet er hidtil uafdækket. Vores studier viser, at plastik kan substituere glaskapillærrør. En kort holdbarhed på maksimalt 10 minutter på plastikkapillærrør er for mange klinisk biokemiske afdelinger er en stor udfordring. Denne holdbarhed kan udvides til 30 minutter uden klinisk forskel for patienterne.

35 - The contact activation system and ulcerative colitis

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INTRODUCTION:
Ulcerative colitis (UC) is an inflammatory bowel disease characterised by recurring exacerbations. Early detection and treatment of exacerbations is essential to obtain the best possible prognosis. Previous research describing the contact activation system (CAS) as a proinflammatory mediator in UC needs further validation. We therefore characterise CAS in UC using new methods focusing on the dynamic interactions, total capacity and endpoint activity of CAS in blood. This may reveal novel biomarkers or treatment targets that can improve UC management.
MATERIAL AND METHODS:
We include and follow 102 adults with active UC. Patients are their own controls during follow up and they are also compared to a non-UC cohort. Exclusion criteria are preselected conditions and non-UC medication influencing CAS or UC activity. There are 4 visits: Week 0 (inclusion), 6, 12 and 26. We collect plasma, stool and colonic tissue samples. We measure coagulation factor XII, prekallikrein, H-kininogen, plasma kallikrein cleaved H-kininogen (cHK), C1 inhibitor and kallikrein generation.
RESULTS:
Preliminary results. 14 out of 28 patients reached endoscopic remission at week 26. There were no significant differences in the groups' demographics. Interestingly, cHK plasma levels were higher in those achieving remission compared to those who are not. The levels of the other CAS proteins did not differ significantly.
CONCLUSION:
Our preliminary results suggest the endpoint marker of CAS activation, cHK changes in relation to UC activity. We believe cHK could be a novel potential biomarker that may improve UC management. Sufficiently powered results are expected later this year.

36 - Associations between education level, blood-lipid measurements and statin treatment in a Danish primary health care population from 2000 to 2018

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Objective:
To examine whether education level influences screening, monitoring, and treatment of hypercholesterolemia.

Subjects:
Cholesterol blood test results ordered by general practitioners in Greater Copenhagen were retrieved from 2000-2018. Using the International Standard Classification of Education classification, the population was categorized by length of education in three groups (basic education; up to 10 years, intermediate education; 11-12 years, advanced education; 13 years or more). The database comprised 13,019,486 blood sample results from 653,903 patients.

Main Outcome Measures:
Frequency of lipid measurement, prevalence of statin treatment, age and comorbidity at treatment initiation, total cholesterol threshold for statin treatment initiation, and achievement of treatment goal.

Results:
The basic education group was measured more frequently (1.46% absolute percentage difference of total population measured [95% CI 0.86%–2.05%] in 2000 and 9.67% [95% CI 9.20%–10.15%] in 2018) over the period compared to the intermediate education group. The advanced education group was younger when receiving first statin prescription (1.87 years younger [95% CI 1.02–2.72] in 2000 and 1.06 years younger [95% CI 0.54–1.58 in 2018) compared to the intermediate education group. All education groups reached the treatment goals equally well when statin treatment was initiated.

Conclusion:
Higher education was associated with earlier statin prescription, although the higher educated group was monitored less frequently. There was no difference in reaching treatment goal between the three education groups. These findings suggest patients with higher education level achieve an earlier dyslipidemia prevention intervention with an equally satisfying result compared to lower education patients.

37 - Total og albumin korrigeret calcium har dårlig korrelation med ioniseret og flere misklassifikationer ved lave og høje albumin niveauer.

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Introduktion
Hvilken metode til måling af calcium i plasma, der er mest optimal, har været diskuteret flittigt gennem tiden. Ioniseret calcium(iCa) i plasma betragtes som guldstandarden. Alligevel er den almindelige metode til at måle calcium Total calcium(tCa), da iCa er både dyrt og besværligt at måle. Formler for korrigeret calcium(kCa) prøver at udregne en mere korrekt værdi af calcium i serum end tCa. Dette studie undersøger korrelationen af tCa og kCa med iCa ved forskellige albumin niveauer, samt korrektheden af hypo-/hypercalcæmi klassificeret af tCa/kCa sammenlignet med iCa.
Metode
Unikke patienter med samtidig måling af iCa, tCa, kCa og albumin fra 2017-2020 i Region Hovedstaden blev trukket fra laboratoriesystemet. kCa blev udregnet fra en lokal tilpasning af Paynes formel. R2 koefficienter for regressioner for iCa med tCa og kCa blev udregnet ved forskellige albumin niveauer. Korrekt klassifikation af hypo/hypercalcæmi blev sammenlignet ved forskellige albumin niveauer.
Resultater
1834 unikke patientmålinger blev undersøgt. Regressionen viste bedst sammenhæng mellem iCa og tCa/kCa ved albumin <35g/L (R2 0.80-0.90), og dårligere ved albumin 35-40g/L (R2 0,74) og >40g/L (R2 0,58). Andelen af fejlklassificerede var samlet set højere for kCa(25%) end tCa(21%). Andelen af fejlklassificerede var højest ved albumin <30g/L med 31%, primært ved hypocalcæmi, og >40g/L med 22%, primært ved hypercalcæmi, og stigende med højere og lavere albuminniveauet. Færrest fejlklassificeringer sås ved albumin 30-40 g/L med 16 %.
Konklusion
Ved højt albuminniveau sås overraskende den dårligste sammenhæng mellem tCa/kCa og iCa. Både ved højt og lavt albuminniveau var der flere fejlklassificerede hypo/hypercalcæmier og flere ved kCa.

38 - MicroRNAs as potential biomarkers for differentiating latent from active tuberculosis

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INTRODUCTION:
Tuberculosis (TB) is an infectious disease that mainly affects the lungs. Infection with Mycobacterium tuberculosis (Mtb) may result in latent or active tuberculosis. The infection is termed (latent) tuberculosis infection (TBI) if no symptoms of disease are observed and there is no evidence of active TB. Early and accurate diagnosis of active TB is critical to enhance patient care, improve patient outcomes, and break transmission cycles. Traditional biomarkers cannot predict who will progress from TBI to active TB. In the present study, we identified differentially expressed microRNAs (miRNAs) in plasma samples from patients with TBI and active TB. We investigated their potential to function as noninvasive predictors of tuberculosis progression.

MATERIAL AND METHODS:
TaqMan low-density arrays (TLDAs) were used to screen the expression level of 754 miRNAs in plasma samples from patients with TBI (n=18) and patients with active TB (n=18).

RESULTS:
The expression levels of ten miRNAs (hsa-miR-139-5p, hsa-miR-146a-5p, hsa-miR-148a-3p, hsa-miR-374b-5p, hsa-let7a-5p, hsa-let-7f-5p, hsa-miR-1301-3p, hsa-miR-188-5p, hsa-miR-22-5p, and hsa-miR-33a-5p) were significantly decreased or increased in plasma from TBI patients compared to TB patients. We evaluated a model based on these miRNAs by receiver operating characteristic (ROC) analysis.

CONCLUSION:
We found that altered expression of certain miRNAs differentiated between TBI and TB, suggesting that plasma miRNAs have the potential to function as noninvasive predictors for TB progression.

40 - Laboratoriediagnostik af Medfødte Fibrinogensygdomme

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Introduktion
Medfødte fibrinogensygdomme (MFS) omfatter fibrinogen defekter karakteriseret ved mangel og/eller dysfunktionelt fibrinogen, som følge af mutationer i fibrinogen genet. Patienter med MFS diagnosticeres ofte et tilfældigt uventet fund ifm. koagulationsscreening. Emnet og terminologien af MFS er ikke velkendt i Danmark, hvorfor hensigten her at opsummere den diagnostiske udredning af MFS.
Materialer og metoder
Ved mistanke om MFS er det afgørende at bestemme fibrinogen i plasma med både en funktionel og immunologisk metode. Til bedre bestemmelse af patienternes kliniske fænotype, udføres specialanalyser, der vurderer fibrinkoagels mekaniske og strukturelle egenskaber. Når den fenotypisk af MFS er gennemført, er genotype bestemmelse obligatorisk for at bekræfte diagnosen.
Resultater
De genetiske og kliniske data i litteraturen resultater i en ny klassificering af MFS i flere typer og undertyper. Afibrinogenæmia er karakteriseret ved fuldstændig mangel på fibrinogen, hvorimod der i hypofibrinogenæmia er et proportionelt fald af både aktivitet og stofkoncentrationen af fibrinogen. I modsætning til dette, ses der i dysfibrinogenæmia nedsat aktivitet, men normal stofkoncentration af fibrinogen. Hypodysfibrinogenæmia er karakteriseret af et uforholdsmæssigt fald af både aktivitet og stofkoncentration af fibrinogen.
Konklusion
MFS er komplicerede og sjældne tilstande, som kan medføre blødninger og/eller tromboser. Der er stadig udfordringer med at forudsige fænotypen hos en patient i forhold til genotypen. Specialanalyser der anvendes MFS diagnostik er som udgangspunkt udviklet i forskningslaboratoriet og forefindes i begrænset omfang i Danmark. Ved begrundet mistanke om MFS, kan patienter henvises til Klinisk Biokemisk afsnit, Syddansk Universitet Hospital, Esbjerg, som har opsat de analyser, der er nødvendige for MFS diagnostik.

41 - Vitamin D Deficiency is Associated with Increased Plasminogen Activator Inhibitor-1 in Pregnant Women

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Introduction: Vitamin D deficiency, which is common in pregnant population, has been suggested as a risk factor for thrombosis, though the underlying mechanism is not delineated. Studies investigating the association between Vitamin D and hemostatic system in pregnant women are lacking. Therefore, we hereby investigated the effect of vitamin D deficiency on the prothrombotic profile in pregnant women.

Methods: A cross-sectional study investigating if vitamin D deficiency affects hemostatic profile in pregnant women with vitamin D deficiency (≤50 nmol/L) (n=70) and with a high adequate vitamin D status (≥100 nmol/L) (n=59). Biomarkers from primary hemostasis, secondary hemostasis and fibrinolysis including von Willebrand factor (vWF), fibrinogen, thrombin generation (lag time, endogenous thrombin potential, peak height, time to peak and start tail), factor VIII, plasminogen activator inhibitor 1 (PAI-1), plasminogen activator inhibitor 2 (PAI-2), tissue plasminogen activator, D-dimer, CRP and PAI-1/PAI-2 ratio, used as an index of placental function, ratio were investigated.

Results: In women with vitamin D deficiency, increased PAI-1, PAI-1/PAI-2 ratio and vWF were found. These findings were further adjusted for pre-pregnancy body mass index (BMI), smoking and use of fish oil supplements as these factors varied between groups. After adjustments, PAI-1 and PAI-1/PAI-2 ratio remained significantly increased. However, findings on PAI-2 and WF were no longer significant as smoking seemed to be determining for vWF, whereas BMI had impact on PAI-2.

Conclusions: Vitamin D deficiency is associated with increased PAI-1 and PAI-1/PAI-2 ratio, indicating poor placental function, in pregnant women, which might associated with thrombotic risk and pregnancy complications.

43 - Short-term biological variation of plasma uracil in a Caucasian healthy population

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Introduction: Plasma uracil is a new biomarker to assess the activity of dihydropyrimidine dehydrogenase before cancer treatment with fluoropyrimidine drugs. Knowledge on the biological variation of plasma uracil is important to assess the applicability of plasma uracil as a biomarker of drug tolerance and efficacy.
Material and methods: A total of 33 apparently healthy individuals were submitted to sequential blood draws for three days. On the second day, blood draws were performed every third hour for 12 h. Plasma uracil was quantified by LC-MS/MS. The within-subject (CVI) and between-subject (CVG) biological variation estimates were calculated using linear mixed-effects models.
Results: The overall median value of plasma uracil was 10.6 ng/mL (range 5.6-23.1 ng/mL). The CVI and CVG were 13.5% and 22.1%, respectively. Plasma uracil remained stable during the day, and there was no day-to-day variation observed. No differences in biological variation components were found between sex and no correlation to age was found. Four samples were calculated to be required to estimate the homeostatic set-point ± 15% with 95% confidence.
Discussion and conclusion: Plasma uracil is subject to tight homeostatic regulation without semidiurnal and day-to-day variation, however between-subject variation exists. This emphasizes plasma uracil as a well-suited biomarker for evaluation of dihydropyrimidine dehydrogenase activity, but four samples are required to establish the homeostatic set-point in a patient.