Casual Friday Series

Functional Blood Chemistry Series
Pt. 14: Wastes (II)

A Biogenetix Clinical Presentation

BIOGENETIX.COM

Disclaimer

- *Information in this presentation is not intended to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

Wastes

- Creatinine
- Uric acid
- Bilirubin
- Blood urea nitrogen (BUN)
- Bile Acids

Creatinine - Increased

Cause	Reason	Additional Inquiry
Kidney dysfunction	Poor kidney function leads to decreased filtration and excretion of creatinine, thus elevating serum creatinine levels.	Evaluate other kidney markers, eg BUN.
Dehydration	Hemoconcentration.	Evaluate other dehydration markers.
Increased muscle mass	More muscle means more creatine and thus, more creatinine.	
Hyperthyroidism	Increased muscle breakdown	Evaluate thyroid markers.
High meat intake	Meat contains creatine and thus can lead to increased creatinine levels.	Diet history.
Ketones	Increases creatinine levels considerably by competing for filtration in the liver.	Client history.

Creatinine - Decreased

Cause	Reason	Additional Inquiry
Decreased muscle mass	Less muscle means less creatine.	
Poor dietary protein intake or absorption	Meat contains creatine. Poor protein digestion or absorption can lead to low creatinine levels.	Diet history. GI symptoms.

Interfering Factors	
Elevated	Decreased
High ascorbic acid intake	Increased bilirubin and glucose levels.

Uric Acid - Elevated

Elevated - If uric acid is elevated above either the optimal or laboratory reference range, it is either increased production, decreased excretion, or a combination of both.

Cause	Reason	Additional Inquiry
Gout	Excessive breakdown of purines	Ask about history of gout and/or systemic joint pain
Kidney dysfunction	Poor filtration and excretion of uric acid, thus keeping serum levels elevated	Evaluate BUN, creatinine, phosphorus; urinalysis
Excess alcohol intake	Hepatocellular destruction	Ask about alcohol intake
Starvation and/or extreme calorie restriction	Catabolism of proteins and thus purine	Diet history
Hypothyroidism	Association	Evaluate TSH
Hyperlipidemia	Association	Evaluate cholesterol

Uric Acid - Elevated

Liver dysfunction	Excess destruction of hepatic cells	Evaluate AST, ALT, GGT, Alk Phos, LDH
Hemolytic anemia	Excess destruction of cells	Evaluate CBC markers
Excess consumption of fructose	Excess fructose increases conversion of ATP to inosine; increases synthesis of purines via the pentose phosphate pathway; fructose may also decrease uric acid excretion	Diet journal - this is huge in diabetes cases!
Chronically elevated serum glucose	Association	Evaluate glucose, hemoglobin A1C
Fungal infection	Some researchers consider uric acid to be a mycotoxin produced by yeast and fungus	
Ketogenic diet	May impair ability of kidneys to excrete uric acid due to competition with ketones. Alternatively, acidic urine increases uric acid reabsorption.	Inquire about diet; ketones in urine; CD cases
High supplemental niacin intake		Supplement history
High protein diet	More protein typically means more purine intake and thus uric acid production	Diet journal
Excess acidity	Excess acidity can lead to acidity of the urine, which tends to reabsorb uric acid leading to higher serum levels.	Acidity is often correlated with blood sugar dysregulation; low CO2 levels can indicate hyperacidity

Uric Acid - Decreased

Cause	Reason	
Molybdenum deficiency	Xanthine oxidase is a molybdenum dependent enzyme. Low levels of molybdenum may lead to decreased uric acid production.	Ask about increased sensitivity to smells and/or consumed sulfites/nitrites (molybdenum also used in sulfite oxidase)
Zinc deficiency	May increase urinary uric acid excretion; low zinc can also lead to high copper, which can negatively impact iron (See below)	Evaluate alk phos; skin issues; taste acuity issues
Iron deficiency	May cause relative increase in copper, which may displace iron with uric acid production	Evaluate ferritin, TIBC, CBC markers
Low purine intake (eg vegetarian)		Diet journal
Oxidative stress	Uric acid is an abundant serum antioxidant. If oxidative stress is high, uric acid levels may be decreased.	Evaluate bilirubin and GGT. Low bilirubin and elevated GGT may further indicate oxidative stress.
Excess alkalinity	Generally the more alkaline the blood, the more alkaline the urine, which is associated with higher levels of excretion of uric acid and thus lower serum levels.	High CO2 levels can indicate hyperalkalinity

Bilirubin - Elevated

Cause	Reason	Additional Inquiry
Excess hemolysis	Excess red blood cell breakdown increases bilirubin (indirect/unconjugated).	
Liver dysfunction	The liver conjugates bilirubin. If the liver is not functioning properly, indirect/unconjugated bilirubin will be elevated.	Evaluate liver markers.
Bile duct obstruction	Bilirubin is cleared from the liver via the biliary ducts into the intestines. Thus if the biliary ducts are obstructed, conjugated/direct bilirubin will enter into circulation.	Evaluate alkaline phosphatase and GGT.
Gilbert's Syndrome	Genetic cause of elevated bilirubin.	Ask client if they have a history of elevated bilirubin. If so, likely Gilbert's

Bilirubin - Decreased

Cause	Reason	
Oxidative stress	Bilirubin can act as an antioxidant and thus, oxidative stress may lower levels.	Evaluate uric acid and GGT as well.
Zinc deficiency	Biliverdin reductase is a zinc dependent enzyme and converts biliverdin to bilirubin, thus leading to low bilirubin levels.	Evaluate alkaline phosphatase.

Can vaping increase bilirubin?

Nicotine Tob Res. 2014 Aug; 16(8): 1145–1149.
Published online 2014 May 8. doi: 10.1093/ntr/ntu067
PMCID: PMC4155425
PMID: 24812024

Smoking Cessation Is Followed by Increases in Serum Bilirubin, an Endogenous Antioxidant Associated With Lower Risk of Lung Cancer and Cardiovascular Disease

Stephanie S. O'Malley, PhD,[1,2] Ran Wu, MS,[1] Susan T. Mayne, PhD,[2,3] and Peter I. Jatlow, MD[4]

Although it is widely known that unconjugated bilirubin can be elevated in hemolytic diseases and can be neurotoxic at very high levels in newborns (Watchko & Tiribelli, 2013), unconjugated bilirubin, the primary form of bilirubin circulating in healthy individuals, is also a powerful antioxidant (Rizzo et al., 2010; Stocker, Yamamoto, McDonagh, Glazer, & Ames, 1987) at levels within the normal reference range. Thus, while seemingly counterintuitive, bilirubin has been inversely associated with risk of a number of disorders, including pulmonary disease (Horsfall et al., 2011), cardiovascular disease (Hopkins et al., 1996; Madhavan, Wattigney, Srinivasan, & Berenson, 1997), diabetes (Cheriyath et al., 2010), rheumatoid arthritis (Fischman et al., 2010), colon cancer risk (Zucker, Horn, & Sherman, 2004), and all-cause and cancer mortality (Temme, Zhang, Schouten, & Kesteloot, 2001). Of note, bilirubin concentrations recently emerged from metabolic profiling as the strongest predictor of lung cancer risk in smokers following a multiphase validation study (Zhang et al., 2013).

Nicotine Tob Res. 2014 Aug; 16(8): 1145–1149.
Published online 2014 May 8. doi: 10.1093/ntr/ntu067
PMCID: PMC4155425
PMID: 24812024

Smoking Cessation Is Followed by Increases in Serum Bilirubin, an Endogenous Antioxidant Associated With Lower Risk of Lung Cancer and Cardiovascular Disease

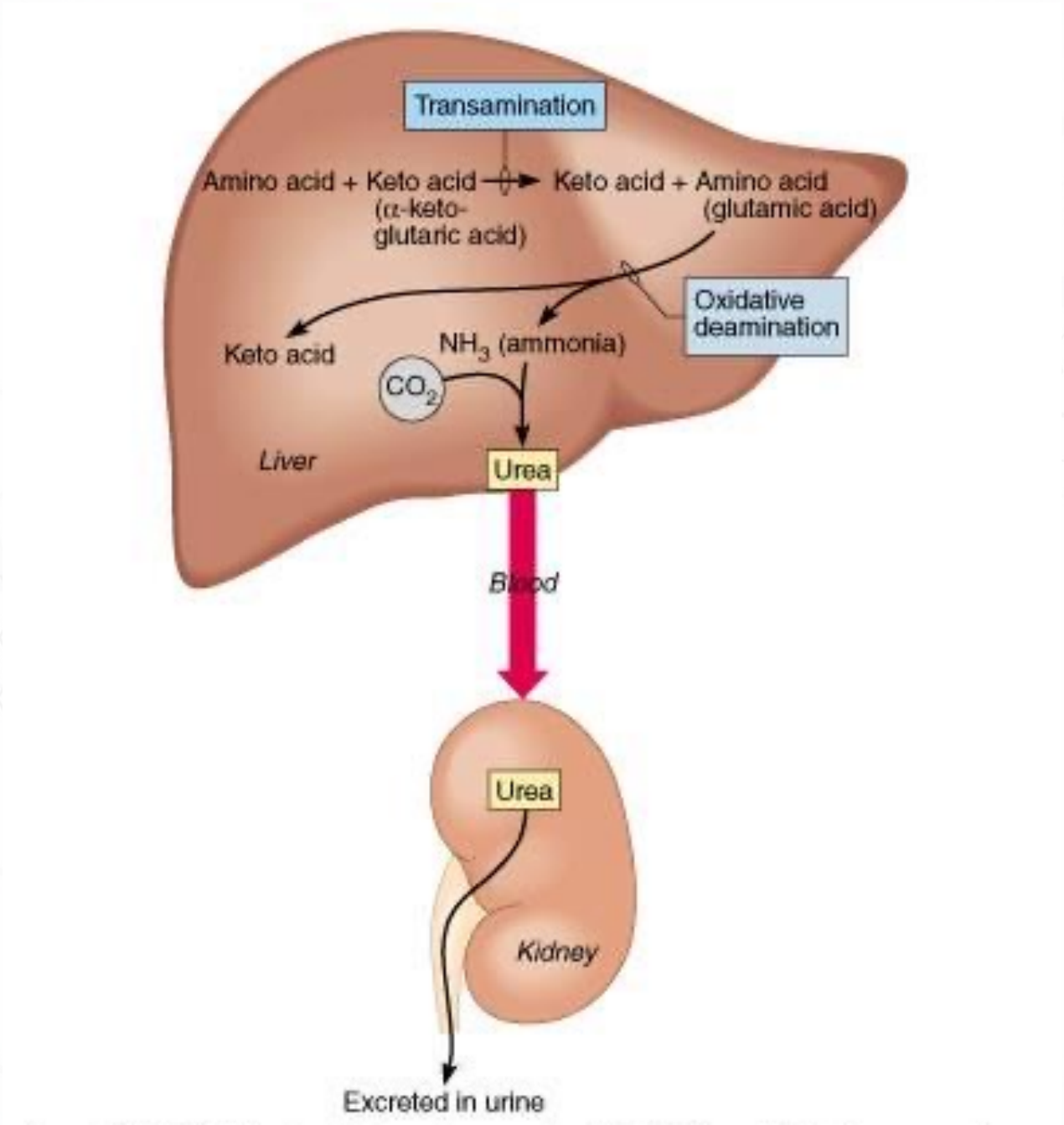
Stephanie S. O'Malley, PhD,[1,2] Ran Wu, MS,[1] Susan T. Mayne, PhD,[2,3] and Peter I. Jatlow, MD[4]

The concordance between the negative health consequences of smoking, including those recently highlighted by the Surgeon General (U.S. Department of Health and Human Services, 2014) and those associated with lower bilirubin concentrations, is striking. Numerous studies have found that smokers have lower bilirubin levels than nonsmokers (Hopkins et al., 1996; Madhavan et al., 1997; Merz, Seiberling, & Thomann, 1998; Van Hoydonck, Temme, & Schouten, 2001; Zucker et al., 2004). The possibility that smoking leads to reductions in bilirubin, which in turn may contribute to smoking-related disease though diminished availability of this endogenous antioxidant, is intriguing. One possible mechanism for bilirubin

In conclusion, our study is the first to document that smoking cessation leads to increases in bilirubin concentrations using a longitudinal design. This finding is consistent with cross-sectional studies suggesting a direct role for smoking cessation in increasing bilirubin concentrations. Moreover, we demonstrate that these changes occur shortly after quitting and posit that these modest increases in bilirubin, an endogenous antioxidant, may contribute to some of the early benefits of quitting smoking.

Blood Urea Nitrogen (BUN)

- Blood Urea Nitrogen (BUN) is the excretory component of protein and amino acid metabolism from the liver.
- Specifically, the liver removes amine groups (NH3) from amino acids, which can create ammonia, which is toxic to the body. Thus the liver synthesizes urea as a means of disposing excess ammonia from the body.
- Urea enters circulation and is excreted via the kidneys.


Transamination
Amino acid + Keto acid
(α-keto-
glutaric acid)
Keto acid + Amino acid
(glutamic acid)
Oxidative
deamination
Keto acid
NH3 (ammonia)
CO2
Liver
Urea
Blood
Urea
Kidney
Excreted in urine

Blood Urea Nitrogen (BUN)

Traditional Reference Range

5-26 mg/dL

Optimal Reference Range

12-17 mg/dL

Blood Urea Nitrogen - Elevated

Cause	Reason	Additional Inquiry
High protein diet	High protein diet leads to more amino acids, which leads to excess urea production.	Client history and diet journal.
Dehydration	Hemoconcentration. Could be secondary to hypoadrenal function.	Evaluate other dehydration markers.
Kidney dysfunction	Because the kidney clears urea, if the kidneys are dysfunctional, urea will build up in circulation.	Evaluate other kidney markers.
Fatty Liver	Mechanism unknown. One study demonstrated that individuals with non-alcoholic fatty liver had elevated BUN.	Evaluate other liver markers. Client history.
Catabolic states	Due to increased amino acid turnover, catabolic states, such as extreme dieting, can cause elevations in BUN.	Client history.

Blood Urea Nitrogen - Decreased

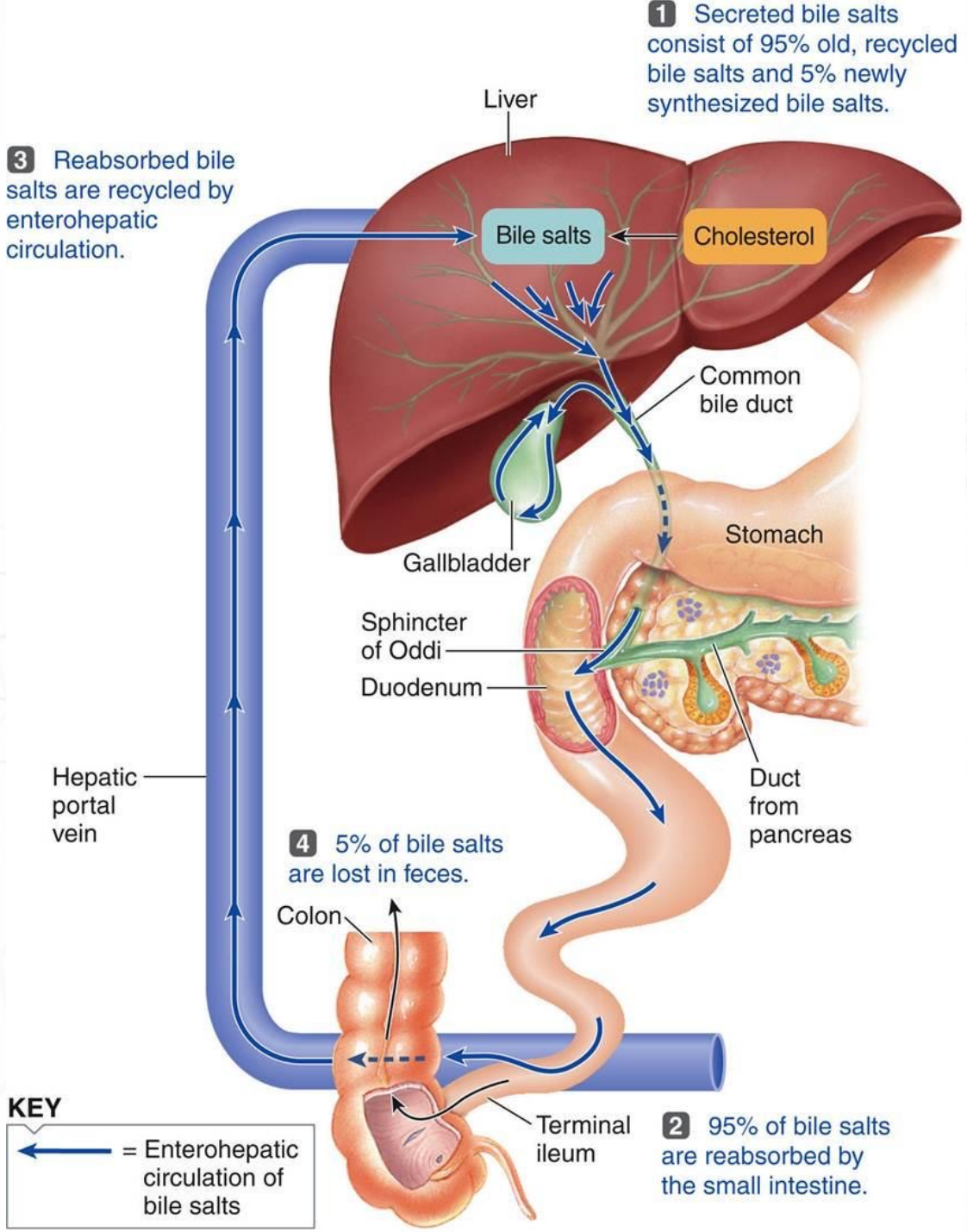
Cause	Reason	Additional Inquiry
Poor protein intake, digestion or absorption	Urea is a byproduct of amino acid metabolism and as such, if protein is low due to intake, digestion or absorption, BUN can be low.	Client history. GI symptoms and function.
Severe liver disease	The liver is responsible for the urea cycle. If the liver is dysfunctional, it will not adequately produce urea.	Evaluate other liver markers.
Possible B6 deficiency	Vitamin B6 (pyridoxine) is responsible for transamination reactions, which is necessary for non-essential amino acid synthesis. Thus if B6 is low, urea may be low as well.	Evaluate AST, ALT and B6 deficiency signs and symptoms.
Excess hydration	Excessive hydration is difficult to attain due to the body's regulatory mechanisms. However hormonal influences can impact this, such as the adrenals and pituitary glands.	

BUN/Albumin Ratio

- The BUN/Albumin ratio has been used clinically to evaluate risk in certain diseased population, such as those with pulmonary disease.
- However, it may have clinical utility in a nutritional practice as BUN can be elevated in dehydration and albumin can be decreased in infection, inflammation, and liver dysfunction, thus increasing the BUN/albumin ratio.
- No studies have been conducted using the BUN/albumin ratio in a nutritional setting but using optimal values for each marker, it would seem a value of <4.0 is desirable.

Bile Acids

- Traditionally understood to be involved in emulsification of ingested fat, allowing pancreatic enzymes (lipase, co-lipase) to breakdown triacylglycerols for absorption in the small intestine
- Involved in the removal of cholesterol, hormones, and toxins


1 Secreted bile salts consist of 95% old, recycled bile salts and 5% newly synthesized bile salts.
Liver
3 Reabsorbed bile salts are recycled by enterohepatic circulation.
Bile salts
Cholesterol
Common bile duct
Gallbladder
Stomach
Sphincter of Oddi
Duodenum
Duct from pancreas
Hepatic portal vein
4 5% of bile salts are lost in feces.
Colon
Terminal ileum
2 95% of bile salts are reabsorbed by the small intestine.
KEY
= Enterohepatic circulation of bile salts

Serum Bile Acids

- A decrease in hepatic blood flow, and/or hepato-celluar damage, or any compromise in liver function will increase serum bile acids
- Test for liver function, where as AST and ALT reflect liver tissue destruction
- Will likely show liver dysfunction well before elevations in liver-based enzymes
- Has highest sensitivity for early stage liver dysfucntion

Serum Bile Acids

- May be of benefit in identifying hepatic dysfunction as a result of chemical or environmental injury
  - 73% of patients exposed to organic solvents had increased TBA (total bile acids), whereas GGT, ALT, AST, and bilirubin were only elevated 8, 3, 2 and 1% respectively
- Useful in minor hepatic derangements

Bile Acids

Traditional reference range:

4.7-24.5 umol/L (LabCorp)

<19 nmol/mL (Mayo)

<10 umol/L (obstetric cholestasis)

Optimal reference range:

4.7-10 umol/L

Bile Acid - Elevated

Cause	Reason	Additional Inquiry
Biliary tree dysfunction	Poor elimination of bile from the liver, through the bile ducts, to the gall bladder and intestines.	Evaluate bilirubin, alkaline phosphatase, and/or GGT. If elevated, may be biliary tree dysfunction.
Liver dysfunction	Hepatic cholestasis, or blockages or liver ducts responsible for the transport of bile.	Evaluate AST, ALT, albumin, BUN.
Decreased GI motlitiy		Patient symptoms; slow transit time

Bile Acid - Decreased

Cause	Reason	Additional Inquiry
Decreased bile synthesis	Poor bile synthesis due to low cholesterol, low taurine/glycine, low reducing agents (NADPH), or liver dysfunction.	Evaluate cholesterol, digestion, and other liver markers.
Bile acid malabsorption	Significant digestive (ileal) dysfunction	Patient history of digestive symptoms.
Increased GI motility		Patient symptoms; increased transit time test

59 yo female, levothyroxine, omeprazole, statin, pain meds.

Comp. Metabolic Panel (14)

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Glucose [01]	88			mg/dL	70-99
	BUN [01]	21			mg/dL	6-24
	Creatinine [01]	0.75			mg/dL	0.57-1.00
	eGFR	92			mL/min/1.73	>59
▲	**BUN/Creatinine Ratio**	**28**	**High**			9-23
	Sodium [01]	136			mmol/L	134-144
	Potassium [01]	3.9			mmol/L	3.5-5.2
	Chloride [01]	96			mmol/L	96-106
	Carbon Dioxide, Total [01]	24			mmol/L	20-29
▲	**Calcium** [01]	**10.3**	**High**		mg/dL	8.7-10.2
	Protein, Total [01]	7.1			g/dL	6.0-8.5
	Albumin [01]	4.7			g/dL	3.8-4.9
	Globulin, Total	2.4			g/dL	1.5-4.5
	A/G Ratio	2.0				1.2-2.2
	Bilirubin, Total [01]	0.4			mg/dL	0.0-1.2
▲	**Alkaline Phosphatase** [01]	**204**	**High**		IU/L	44-121
	AST (SGOT) [01]	17			IU/L	0-40
	ALT (SGPT) [01]	19			IU/L	0-32

57 yo female, basaglar, farxiga, BP meds, Statins.

Comp. Metabolic Panel (14)

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Glucose** [01]	**102**	**High**		mg/dL	65-99
▲	**BUN** [01]	**34**	**High**		mg/dL	6-24
▲	**Creatinine** [01]	**1.65**	**High**		mg/dL	0.57-1.00
▼	**eGFR**	**36**	**Low**		mL/min/1.73	>59
	BUN/Creatinine Ratio	21				9-23
	Sodium [01]	140			mmol/L	134-144
	Potassium [01]	5.0			mmol/L	3.5-5.2
	Chloride [01]	103			mmol/L	96-106
▼	**Carbon Dioxide, Total** [01]	**19**	**Low**		mmol/L	20-29
	Calcium [01]	9.5			mg/dL	8.7-10.2
	Protein, Total [01]	6.8			g/dL	6.0-8.5
	Albumin [01]	4.7			g/dL	3.8-4.9

Urinalysis (No Micro)

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Specific Gravity [01]	1.020				1.005-1.030
	pH [01]	5.5				5.0-7.5
	Urine-Color [01]	Yellow				Yellow
►	**Appearance** [01]	**Cloudy**	**Abnormal**			Clear
►	**WBC Esterase** [01]	**1+**	**Abnormal**			Negative
►	**Protein** [01]	**2+**	**Abnormal**			Negative/Trace
►	**Glucose** [01]	**1+**	**Abnormal**			Negative
	Ketones [01]	Negative				Negative
►	**Occult Blood** [01]	**Trace**	**Abnormal**			Negative
	Bilirubin [01]	Negative				Negative
	Urobilinogen,Semi-Qn [01]	0.2			mg/dL	0.2-1.0
	Nitrite, Urine [01]	Negative				Negative

Homocyst(e)ine

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Homocyst(e)ine** [01]	**16.9**	**High**		umol/L	0.0-14.5

Uric Acid

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Uric Acid [01]	7.0		mg/dL	3.0-7.2
		Therapeutic target for gout patients: <6.0		

The Wedge Protocol