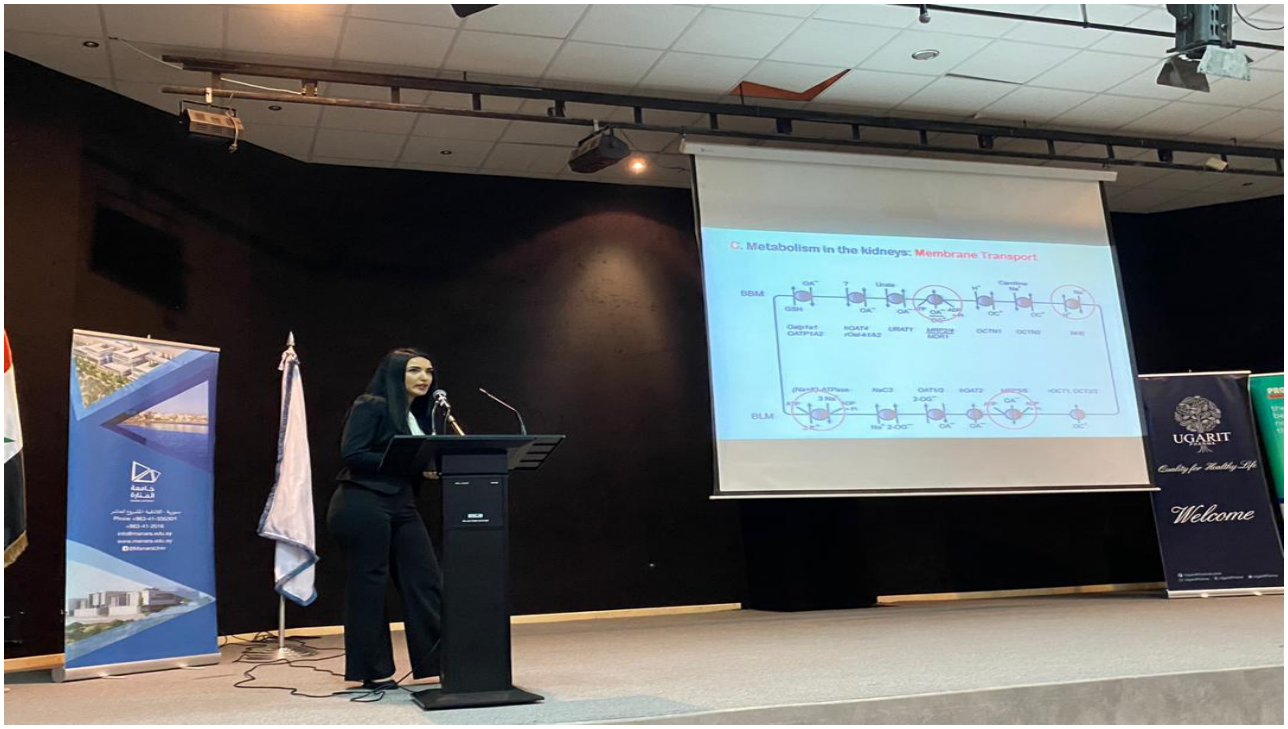
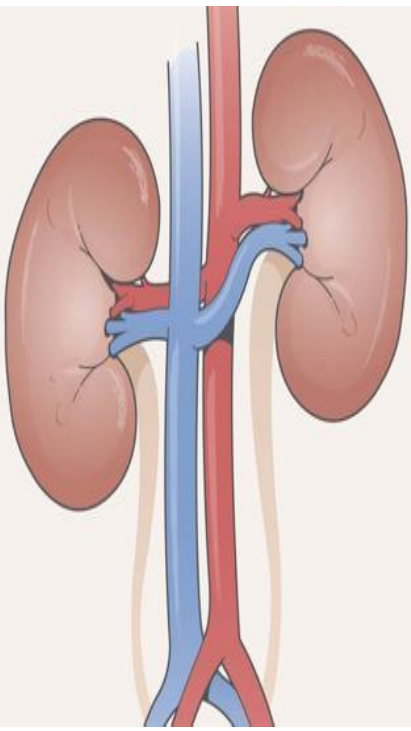
Kidney and drug metabolism

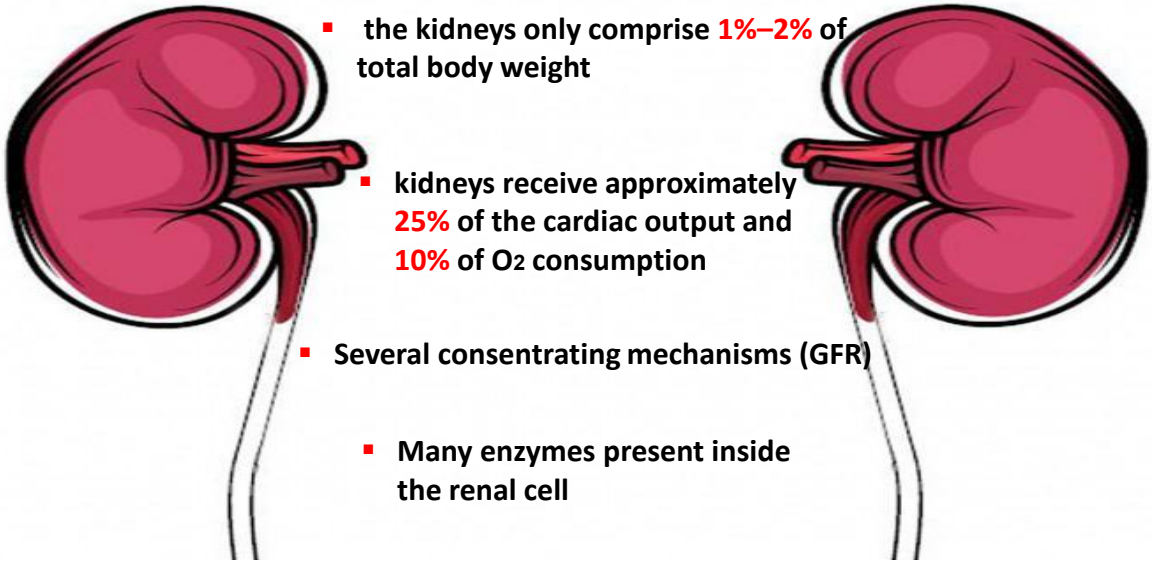
Hala Aldeeb
Postgraduate Studies in Pharmacy, Master





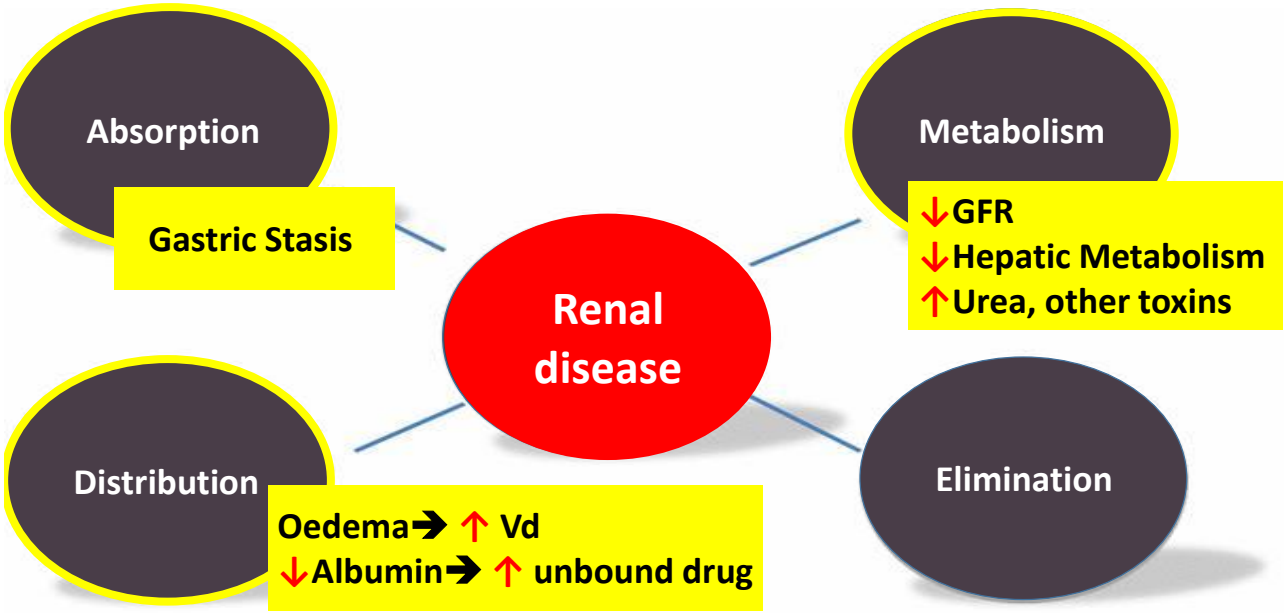
A. Introduction
B. How kidney function affects drug pharmacokinetics
C. Metabolism in the kidneys: membrane transport
D. Metabolism in the kidneys: phase I
E. Metabolism in the kidneys: Phase II
F. Examples

A. Introduction

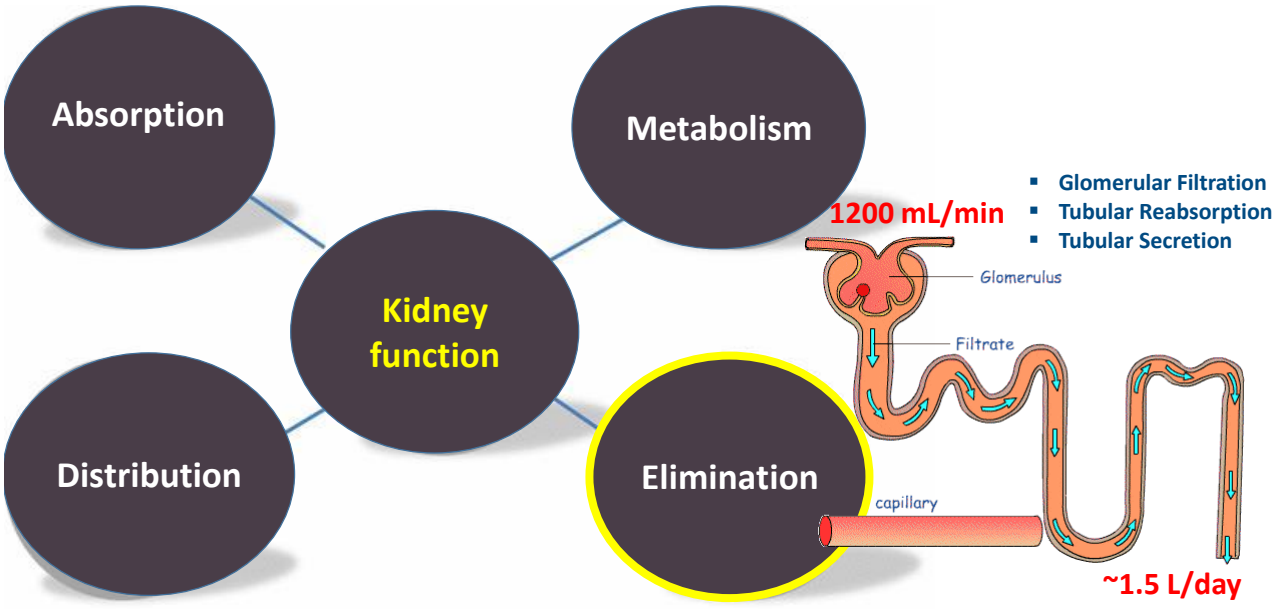


- the kidneys only comprise 1%–2% of total body weight
- kidneys receive approximately 25% of the cardiac output and 10% of O_2 consumption
- Several consentrating mechanisms (GFR)
- Many enzymes present inside the renal cell

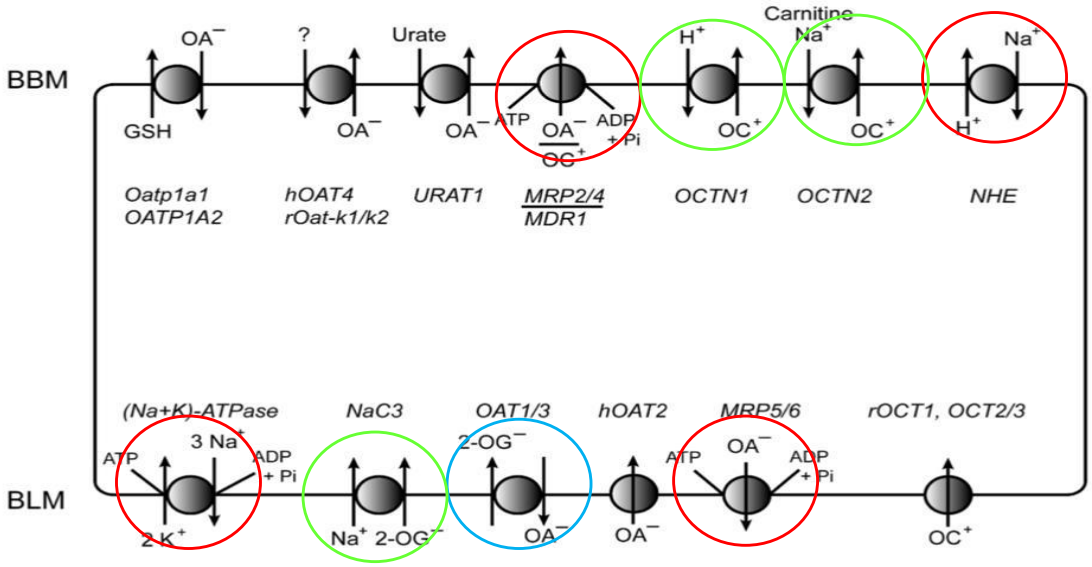
B. How kidney function affects drug pharmacokinetics



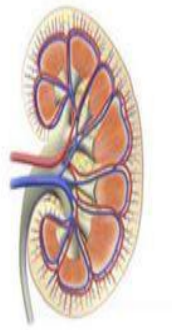
B. How kidney function affects drug pharmacokinetics



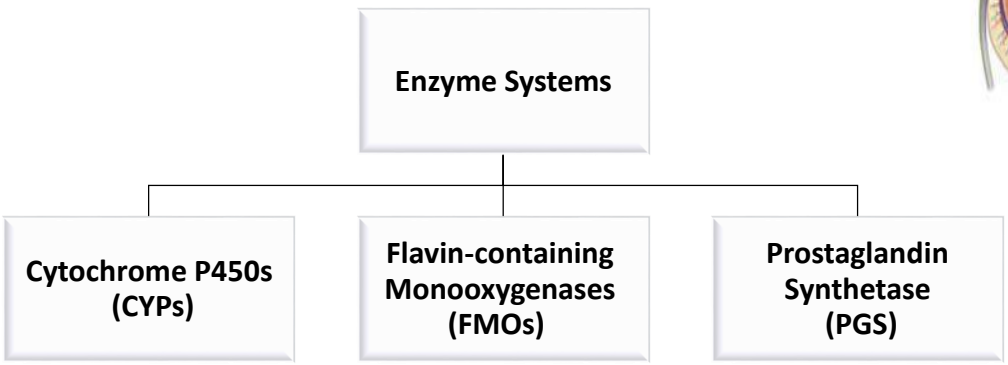
C. Metabolism in the kidneys: Membrane Transport



D. Metabolism in the kidneys: Phase I



- **Phase I enzymes in the kidneys exhibit similar biochemistry as those in the liver**



D. Metabolism in the kidneys: Phase I

➢ **Cytochrome P450s**

CYP Enzyme	Rats and/or Mice	Humans
CYP1A1/2	Low constitutive; CYP1A1 inducible	Not detected or poorly inducible
CYP1B1/2	Present at modest levels	Present at modest levels
CYP2A	Present in mice; not detected in rats	Not detected
CYP2B1/2	Inducible by clofibrate in rats	Not detected
CYP2C11 (CYP2C19)	Constitutive; sex and developmental differences	Not detected
CYP2D6	Low levels	Low levels
CYP2E1	Present; inducible	Not detected or barely detectable
CYP3A1/2 (CYP3A4/5)	Primarily in glomerulus	Glomerulus, proximal tubule; genetic polymorphisms
CYP4A2/3 (CYP4A11)	Proximal tubule; inducible by fibrates	Proximal tubule; inducible by ethanol, dexamethasone

D. Metabolism in the kidneys: Phase I ➢ Cytochrome P450s

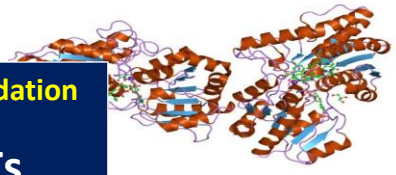
Nephron Cell Type	Morphology	Physiology	Metabolism
Proximal tubule	Tall, prominent microvilli on luminal membrane; cuboidal shape; extensive basolateral infoldings; high density of mitochondria	Active Na^+ reabsorption; organic anion and cation secretion; most glucose and amino acid reabsorption; passive water and Cl^- reabsorption	Oxidative phosphorylation, citric acid cycle, gluconeogenesis; substrates = fatty acids, ketone bodies, lactate, glutamine, pyruvate, citrate, acetate; Drug metabolism: High CYP, FMO, UGT, SULT, GSH-dependent
Thick ascending limb	Extensive interdigitations; large number of elongated, rod-shaped mitochondria	Water-impermeable; Na^+-K^+-$2Cl^-$ cotransport; active Ca^{2+} and Mg^{2+} transport; dilution of hyperosmotic tubular urine	Oxidative phosphorylation and glycolysis; substrates = lactate, glucose, ketone bodies, fatty acids, acetate; Drug metabolism: Low CYP, FMO, UGT, SULT; high PGS (mTAL)
Distal tubule (distal convoluted tubule and cortical collecting duct)	DCT: appears bright under microscope; numerous, long mitochondria. CCT: appears granular under microscope; wider than DCT.	High rates of Na^+ reabsorption; thiazide-inhibitable Na^+-Cl^- cotransport; K^+-Cl^- cotransport; Ca^{2+} reabsorption; DCT: water impermeable; CCT: vasopressin-dependent water channel	Glycolysis; substrates = glucose, lactate, β-hydroxybutyrate, fatty acids (CCT only); Drug metabolism: Generally all low

D. Metabolism in the kidneys: Phase I ➢ Cytochrome P450s

Enzyme	Representative major substrates
CYP1A2	Caffeine, clozapine, dacarbazine, leflunomide, lignocaine, tacrine, theophylline
CYP2A6	Nicotine
CYP2B6*	Bupropion, cyclophosphamide, efavirenz, ifosfamide, ketamine, propofol
CYP2C8†	Amodiaquine, chloroquine, paclitaxel, repaglinide, rosiglitazone
CYP2C9†	Losartan, NSAIDs (e.g. celecoxib, diclofenac, flurbiprofen, ibuprofen), oral hypoglycaemics (e.g. gliclazide, glibenclamide, glimepiride, glipizine, tolbutamide), phenytoin, torasemide, *S*-warfarin
CYP2C19	Citalopram, escitalopram, nelfinavir, PPIs (e.g. esomeprazole, lansoprazole, omeprazole, pantoprazole), proguanil, voriconazole
CYP2D6	Dextromethorphan, desipramine, fluoxetine, nortriptyline, perhexiline, tramadol, venlafaxine
CYP2E1	Enflurane, halothane
CYP3A4†/5*	Carbamazepine, calcium channel blockers (e.g. diltiazem, felodipine, nifedipine, verapamil), cyclosporin, HIV protease inhibitors (e.g. indinavir, lopinavir, ritonavir), ifosfamide, midazolam, statins (e.g. atorvastatin, simvastatin), tacrolimus, triazolam, tyrosine kinase inhibitors (e.g. dasatinib, lapatinib, sorafenib, sunitinib)

*Expressed in human kidney. †Evidence for expression in human kidney equivocal.

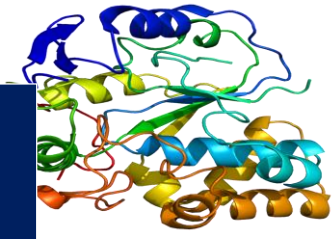
E. Metabolism in the kidneys: Phase II



Glucuronidation

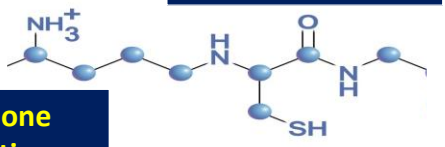
UGTs

- Steroid hormones
- Acetaminophen



Sulfation

SULTs



Glutathione

Glutathione Conjugation

Detoxification

F. Examples Illustrating Unique Functions of Kidneys in Drug Metabolism

- APAP is a widely used analgesic
- Frequent cause of poisoning due to overdose
- Initial site: LIVER
- Secondary sites: KIDNEYS

APAP Over-dosage	Tubular necrosis
Chronic ingestion of APAP	Papillary necrosis Interstitial fibrosis

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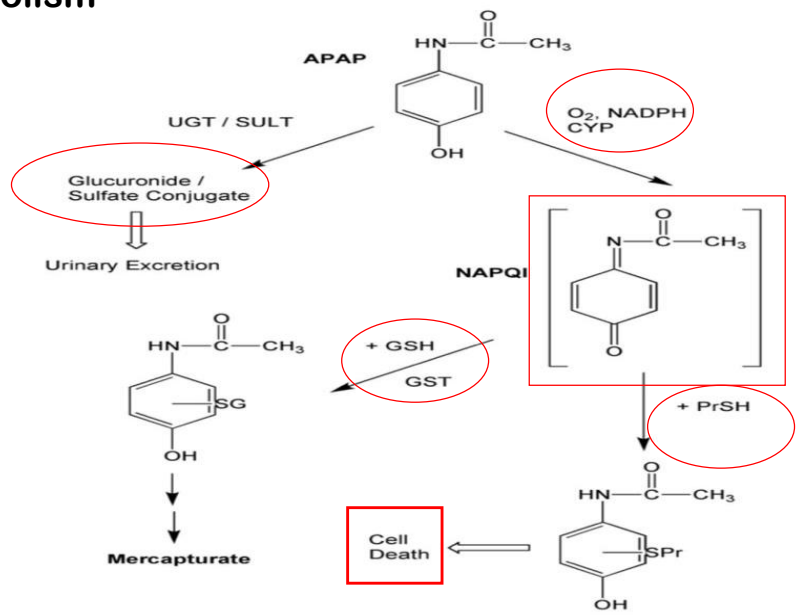

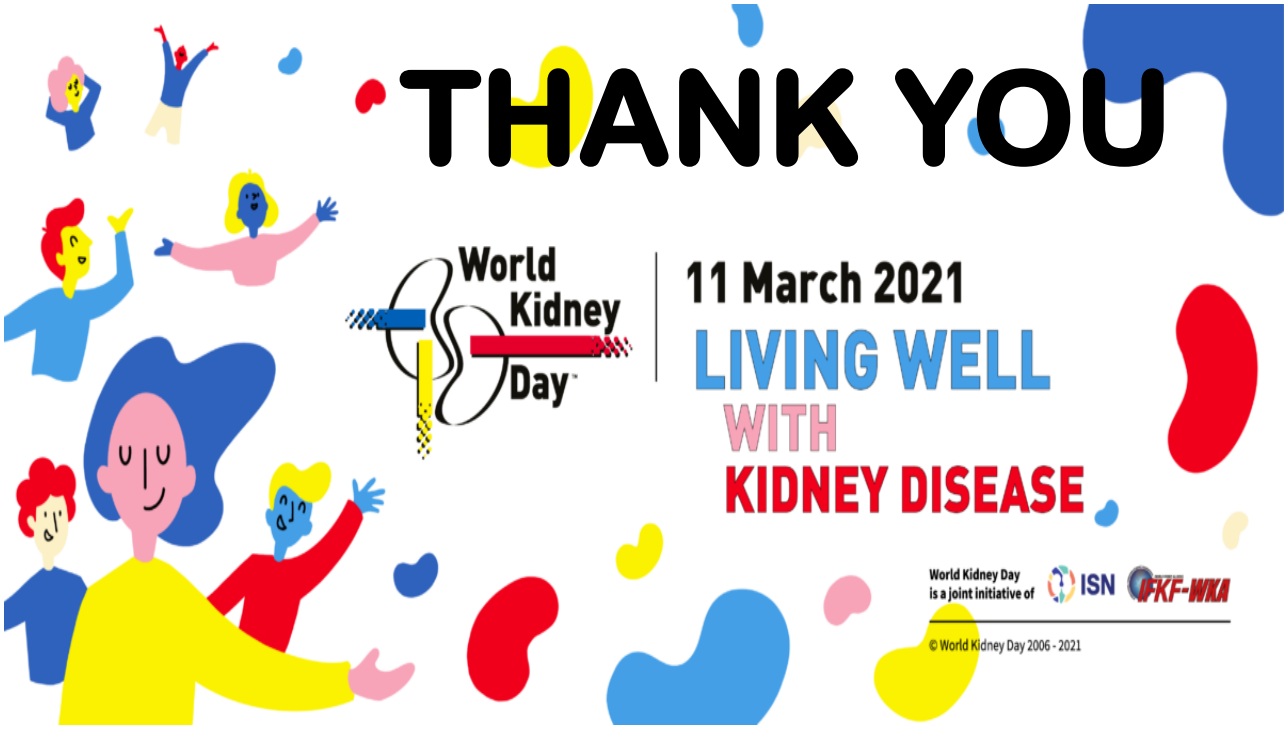
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World Kidney Day
11 March 2021
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WITH
KIDNEY DISEASE
World Kidney Day is a joint initiative of
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