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3.2. Anukta Vyadhi Vichar:-

As mentioned in Charak sutrasthana trishothiyadhyya that all diseases can’t labeled with some name. The diseases can be studied as a kupita dosha, specific causes and their sites. Considering vyadhi prakruti-ashaya i.e. sthana is important for nidana and chikitsa.

The vyadhi mentioned in samhita with its specific samuthana (causes) which are responsible for aggravation of doshas. The samuthana leads to ashaya / sthana (site) in particular for the expression of vyadhi such as amashaya and Pakavashaya. The vyadhi is having its own akruti (shape) such as Gulma and Arbuda. The labeling or nomenclature of single disease as Rajayaksha / Shosa is mentioned in samhita. The Sthula vikara are grossly classifiable in Udara, Mutrakruchha but remaining asthul vyadhi should be considered as prakrutsamanyam i.e. causes and dosha dushti according to it. Then it is named as per dominance of doshas and dhatus vata, pitta or kaphaj or rasa, rakta respectively.4

The Anukta Vyadhi concept as elaborated in laghanbhrrubaniya adhya Sansarg and Sannipat may be of various types of various chikitsa are mentioned individually or grouped (sankirnata) respectively. As mentioned in langhanbhrruniya adhaya though the pattern and types of chikitsa are different grouped into only six types laghan & bruhan. Thus the method to study the Anukta Vyadhi is to study the causes, dosha and sthanas respectively.5

The vatadi dosha sansarg and sannipat are of different types but the doshas are of only three though the vyadhi is anukta but it can be classified on the dominance of dosha or doshas involved.

The Anukta Vyadhi is priory swatantra having its own potential after that it may cause other vyadh. In that case one disease is cause for other disease.6

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4 Ch. Su. 18/45, Page 108.
5 Ch. Su. 22/43 Page 122
6 Ch. Ni. 8/21-22, Page 228
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Vyadhi avastha or Anukta Vyadhi can be studied as minute changes in i.e. vruddhi, kshaya and sthana. As well sharir, Agni, bala and state of kshaya, vruddhi and sthana are to be studied particularly. 7

**Vyadhi and Lakshana Relation:-**

The vyadhi is group or individual lakshana evidence. In Anukta vyadhi the disease in not specifically labeled it is group of lakshana and may be labeled as lakshana samuchya. Thus the symptom complex is not labeled as a disease as it is having some disease in past history. 8

In particular disease / vyadhi the - Prakopa, Yoni-uthana, Atma, Adhisthana, Vedana, Sansthana, Shabda, Sparsha, Roopa, Rasa, Gandha, Upadrava, Vruddhi, Sthana, Kshaya, Udaraka, Chikitsa are considered. Same with Anukta Vyadhi these are the highlighting points to assess the symptom complex as it is not labeled with specific name. The same methodology is implemented to study here to deal with CKD.

Dushit doshas are main causes for all diseases. All the different kinds of diseases cannot be devoid of the doshas. Even though, those caused by dushta dhatus, cannot be without the involvement of the doshas. 9

The physician should never feel shy for not knowing the nomenclature of the disease, for these there is no rule/ custom/ state that every disease has a name. The very same dosha, depending upon the nature of the causes circulate to other parts of the body and produces many diseases hence treatment should be targeted determining the nature of the disease site and its causes. 10

To study Anukta Vyadhi these methods are illustrated in samhita. Thus to study aetiopathogenesis of CKD, these pathways are used. Such as dosha prakopa, vruddhi, Sthana, Lakshana, Samuthana causes are studied.

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7 Ch. ni. 8/36, 37, page 229
8 Ch. ni 8/40, page 229
9 A. Hr. Su. 12/32, page197
10 A. Hr. Su. 12/ 64-66, page 206
So, considering all above information related to CKD, it suggests dealing with CKD Ayurveda aspect in the same way. These are the sthana (Vrukka – Sharir, Sharir Kriya, Involved Dosha, Agni, Dhatu etc.) same methodology is followed in the wholesome study. Particularly Kleda, Mutra, Sweda, Pakawakshaya, Agni & Pachana are important among them.

**Sharir – Basti, Vrukka, Gavini, Mutravaha Strotas**

As stated in Khudika Garbhavkranti Adhyaya formation of Garbha is due to Shukra & Artava. Matruja bhava is one of the six bhava of Garbhotpathi. Matruja Ahara rasa nourishes Garbha eventually ends in the formation of individual.

Twaka, Nabhi, Hridya, Kloma, Yakruta, Pliha, Vrukka, Vasti, Purishadhana, Amakshaya, Pakawakshaya, Uttar and adharguda, Shudrantra, & Vapa are maturja organs.11

**Vrukka – Matruja Avayava:-**

The twak lohit, mamsa, meda, nabhi Hrudya, klom, yakovrt, pliha, vrukka, basti and purishadhana are maturjavayuva.12

**Vrukka and Mahabhuta Relation:-**

<table>
<thead>
<tr>
<th>Pruthavi</th>
<th>Vrukka akara</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jala</td>
<td>Kleda and Mutra</td>
</tr>
<tr>
<td>Tej</td>
<td>Tej mahabhuta for blood filtration with formation of mutra</td>
</tr>
<tr>
<td>Vayu</td>
<td>All functions of vrukka</td>
</tr>
<tr>
<td>Akasha</td>
<td>Maintains sachidrata –porosity.13</td>
</tr>
</tbody>
</table>

**Vrukka and Dhatu: -** Vrukka is formed from Rakta and Meda dhatu mainly.14

**Vrukka Mulsthana: -** Vrukka is mulsthana for Medavaha Strotas.15

**Vrukka – Dosha: -** Tridosha with Kapha dominances.

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11 Ch. Sh.3/6, page 310
12 Su. Sa. 4/31
13 Ch. Su. 26/11, page 138
14 As. Sa. 5/28
15 Ch. Vi. 5/8, page 251
**Strotas hetu and dushti lakshana:**

**Medovaha Strotas:** Day sleep, Fatty food and Alcoholic drinks.

**Dushti Lakshana:** Prameha Purupa.

**Mutravaha Strotas:** The basic site for mutravaha Strotas is muttrashaya and vankshana.

**Dushti lakshana:** Bahumutrata, Alpamutrata, Mutra Avarodha, Buring Urination, Mutra Gandha, Varna changes.

**Purishavaha Strotas:** Pakawakshaya and guda

**Purisha Strotas Lakshana:** Shashoola, Sakashta, Sarakta, Pravartana.

**Swedavaha Strotas:** Meda and lomakup

**Dushti lakshana:** Daha, lomaharsha, excess sweating, less sweating dryness of skin.

**Dosha & Mutra:-**

The tridosha nirmiti in the body is output of digestive process that is pachana. Here pachana means it is of the Ahara taken by individual for his daily energy requirement. The daily diet consumption is processed through pachanasansththa. This is directly related to the basic three avasthapakas respectively forming prakrut kapha, Pitta & Vata. Further the remaining (Pachit Ahara rasa) part after formation of the tridoshas is directed / circulated throughout the body. During this process the particular dhatus take necessary part for their poshana individually.

This is the basic pachana process in digestive system labeled as three avasthapaka which is not possible without kayagni.

The rest remaining part is already having mala in avyaktarupa where mutra is also avyakt in jaliya form as it is with the dhatuposhanka ghatak.

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16 Ch. Vi. 5/8,14-16, page 250,251
The same rasa circulating throughout the body nourishes the individual dhatu with their respective ghatak. Hence this is the sukshma pachana nourishing the dhatus. The jaliya part again in avyakta form is given back to the circulating rasa.

Here during sukhsha pachana meda dhatu is the chief among the seven dhatus which contributes on higher side for kleda formation.

Thus sthula pachana is occurred in pachana sansthna level & sukshma pachana is at dhatu level, simultaneously form the avyakta mutra which at terminal stage is given vykta mutra form at mutrakshaya level. (Vrukka – vasti)

Formation of Urine:-

Saman Vayu facilitate pachana with the help of Kledaka Kapha to reduce the Kledan karma facilitate Pachaka strava from Amashaya, Pachamanasahya, Yakrut and Agnyashaya. This helps in formation of Teja, Drava and sukshma Ahara and separation of mala into Saara & kitta. The ahara rasa absorbed by Grahani and forwarded towards heart (by rasa dhamanya for further body nourishment).17

This antrapachan gives rise to dosha formation. The dosha similar guna ghataka absorbed in rasa and nourishes for dosha. This is the vital function of Samaan Vayu.

Samaan Vayu Prakupit Vikaras are Gulma, Atisaara and Agnimandya etc.

Mutra Pravartara Excretion urine18

The apana vayu site is Vrushna, Vrukka, Basti, Gavini, Nabhi, Uru & Guda.19

When the bladder is completely filled with urine, it is excreted with the stimulus of Apana Vayu.

Apana Vayu Prakupita Vyadhi:

The apana vayu vitiation leads to Mutragrha, Garbhastrava and Bhagandra.20

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17 Va. Su. 12/8, page 55
18 Va. Su. 12
19 Ch. Chi. 28/10, page 616
20 Su. Ni. 1
Pitta dosha:
Pitta vruddhi Lakshana – This leads to yellow coloration of mutra.\textsuperscript{21}
Pittakshaya: The functions of pachak pitta is hampered due to which Agnimandya & Anannabhilasha and the whole body get pale due to kkshaya of pitta.

Yakrut in Mutra Nirmiti:

Amashaya Grahani, Pakawashaya and their respective avasthapaka -Madhur, Amla & Katu. This ahara rasa formed in avasthapaka basically circulated from Yakrut to heart. The state of ahara rasa depending upon which type of ahara is taken is processed by Yakrut. The function of Yakrut is to maintain ahara rasa Atisukshma & Saarabhu in nature. Remaining portion which is not completely pachit is cleared by Yakrutastha Agni. The kitta paramanu formed in Yakrut mix with kleda and excreted as mutra.\textsuperscript{22}

Rakta Dhatu: Functions of Rakta dhatu are Varna Prasadana, Indriya Prasadana, Indriya vishaya grahana & timely excretion of mala.\textsuperscript{23}

Meda dhatu:

The Meda dhatu nirmiti is followed by mamsadhatu with the help of medadhatuagni. Meda dhatu consists of jal mahabhuta dominant aliment and sneha dominant aliment. The sira and snayu are updhatu of meda.\textsuperscript{24}

Vruka mutra and sweda:

The kapha & meda properties are approximately same in nature. The kleta portion of kapha partly store in meda dhatus when needed used by sharir. As well if this kleta becomes excess stored in Vrukka and regulated as mutra & sweda. The sneha of majjadhatu keeps Twaka Varna in prakrutika condition. It helps in raktotpatti with Yakrut, Pliha & Sira.

\textsuperscript{21} Va.Su. 11/7, page 52
\textsuperscript{22} Doshadhatu malavidgyma page 102.
\textsuperscript{23} Ch. Su. 24/24
\textsuperscript{24} Su. Sh.
Pachana and Mutra roga:

The Abhojana Ajeerna, Atibhojana, Vishmashna, Asatmya, Guru, Sheet, Rooksha bhojana leads to disturbances of Agni. The dushtagni is unable to digest laghuahara too; Disturbed pachana gives shuktatva to ahara forming Aharvisha. The portion leads to Mutrsanga and Mutravikara.\(^{25}\)

The above mentioned hetus for Agni dushti are responsible for pachan vikruti. Also the dushti ahara rasa with vyana vayu circulated throughout –Sharir. The vikruti observed in sthana vaigunaya.\(^{26}\)

This leads to rasa dhatu dushti. This dusshit rasa dhatu with vyana vayu circulated throughout body. It is lodged where basic vaigunaya i.e. Khavaigunya is present.

Krimi Pachana– (Lakshane samuchya seen in pt)

The kshira, guda, tila, matsaya (anoop), pistanna, jreerna, puti, klinna, viruddha ahara, leads to shlemajakirmi. These krimi gives rise lakshanas such as Murchha, Jrumbha, Aanaha, Agmarda, Chhardi, Karshya and Parushya.\(^{27}\)

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\(^{25}\) Ch. Chi. 15/49, page 517

\(^{26}\) Ch. Chi. 15/36, page 516.

\(^{27}\) Ch. Vi. 7/12
Mutra and Kleda:-

The pachana of ahara is passed through Avasthapaka.

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Ch. Su. 6/14, page 332

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28 Ch. Su. 6/14, page 332
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Kleda and Prameha:

The sharistha kleda is mixed with shleshma and meda. This is driven toward muttrakshaya. The properties such as shewta, sheet, murt, pichil, snigdha, madhur, Sandra leads to type of Kaphajmeha.29

Kleda and Vata rakta: - The dushit kleda and vata results in vata rakta.30

Kleda & Pitta: The kleda with shonit leads to tanutva of rakta dhatu.31

The mamsa kleda leads to pittaroga.32

Kleda Rasa: -

The lavana rasa with dushit kleda gives rise to mutra daha, as Lavana rasa is basically ushna, tikshna and upa-kledi.33

Kleda Madya:

The excess madya sevana leads to Vidahi, Vidagdha and Kleda Vruddhi causing ksharatva.

Sweda:

Sweda-Mutra- Upadrava:

The dushti of vata dosha leads to pachana sweda and mutra avarodha. The dushit vayu with urdhva gamitva causes Strotas avarodha of meda, sweda, mutra and ambu (uadaka). This gives rise to Chhardi, Hikka, and Shwas.34

Sweda and kleda: - The sweda protects the roma as well twak sneha.35

Swedavaha Strotas Dushti Lakshana:

The dushti lakshana of swedavaha Strotas are twakparushatva, aswedsna, excess sweda, Paridaha, Lomaharsha.

29 Ch. Chi. 6/51
30 Ch. Chi 29/27, page 629
31 As. Sa. Su. 20/10
32 Ch. Su. 20/14
33 Ch. Su. 26/67
34 Ch. Chi. 20/16, page 556
35 As. Su. 19/2
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Sweda vruddhi Lakshana: - Sweda vruddhi lakshana are kandu & gandha vikruti.\(^{36}\)

Manasaguna Sweda:-

The viharia hetu Vyayama, krodha, sheet followed by ushnas & shoka leads to sweda dushti.\(^{37}\)

Sweda vrudhi & sweda kshina lakshana:-

Sweda vrudhi leads to kandu and daurgandhya. Sweda kshaya leads to hair fall, and dry scaly skin.\(^{38}\)

Harita samhita:-

Harita samhita mentioned Arishtas lakshanas of Ashamari, Prameha, and Pandu vyadhi. The Pandu vyadhi Arishtas are Shopha, Shwas, Pipasa, Shoola. The Prameha Aristas are excessive stravas and Prameha pitika.\(^{39}\)

Rajnighantu:-

Rajnighantu mentioned mutra dosha –Prameha, Mutra Kruchha, Mutra Rodha is labeled as mutra ashmari.\(^{40}\)

**Pakvasaya sharir:**

Pakvasaya is matruja avayva it is a site of vata. The dhamnaya of Pakvasaya carry Vata, Pitta & Kapha Dosha, Udaka, Mutra, Shuddha Rakta, Shukra, Artava and Purisha. The dushit dosha in Pakvasaya leads to Kati Shotha.\(^{41}\)

The Pakvasaya is udbhava sthana of hikka. The apana prana vayu leads to hikka.

**Vega:** The Vega vidharana of adharaniya vega is one of the dushti cause of mutravaha Strotas.

\(^{36}\) Va. Su. 11/14  
\(^{37}\) Ch. Chi. 15/239  
\(^{38}\) Va. Su. 11/22  
\(^{39}\) Ha. Sa. 2/4124  
\(^{40}\) Ra. Ni.  
\(^{41}\) Su. Chi. 23/6
**Dharaniya:** The significance of Dharana – to settle, restore for some time is dharana.

It may be the kayic, vachic and manasic.

**Adharaniya:** There are thirteen adharaniya Vegas are mentioned. Mutra, Mala, Shukra, Apana, Chhardi, Shvyathu, Udagara, Trishana, Shudha, Jrumbha Ashru, and Nidra, Shramashwasa.

**Mutra Vega vidharana lakshana:** Vasti, vinama, mutra krushratva, shirashoola and vanshana anaha.

**Mala Vega vidharana lakshana:** Shirashoola, Malavabaddhata, Pindikodweshatan, Adhamana.

**Apana vayu vidharana lakshana:** The Vata, Mutra Mala Sanga, Adhamana, Klama, Udarshoola and Vata Vikara.

**Chhardi Vega vidharana:** Kandu, Kotha, Aruchi, Vyanga, Shotha, Pandu, Jwara, Kushta, Hrullasa and Visaarpa

**Shvayuthu Vega vidharana lakshana:** Manyastambha, Shirashoola, Ardit, Ardhavabhedaka and Indriyadrubalya.

**Udagara Vega vidharana:** The Hikka, Kasa, Aruchi, Urogaurava seen.

**Jrumbha Vega vidharana:** Vinama, Akshepa, Sankocha, Supti, Kampa seen

**Shudha Vega vidharana:** Karhsya, Daruballya, Vaivaranya, Agagmarda, Aruchi, Bhrama seen.

**Trishana Vega vidharana Lakshana:** Kantha and Mukha Shosha, Badhiraya, Shrama, Angasada, Hrudavedana.

**Ashru Vega vidharana:** Pratishya, netravikara, hrudvikara as well aruchi, bhrama.

**Nidra Vega vidharana:** Jrumbha, Aganmarda, Tandra, Shirogaurava and Netra Gaurava.
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**Shramashavasa:** Gulma, Hrudroga, Samhoha

**Dharaniya Vega:**

- **Manasa Vega:** Lobha, Shoka, Krodha, Ahankara, Irsha.
- **Vachic Vega:** Bhashana, lies and all.
- **Sharirik Vega:** Stealing,
3.3. Physiologic Anatomy of the Kidneys:

Kidneys and Urinary tract:-

The two kidneys lie on the posterior wall of the abdomen, outside the peritoneal cavity (Figure). Each kidney of the adult human weighs about 150 grams and is about the size of a clenched fist. The medial side of each kidney contains an indented region called the hilum through which pass the renal artery and vein, lymphatic, nerve supply, and urethra, which carries the final urine from the kidney to the bladder, where it is stored until emptied. The kidney is surrounded by a tough, fibrous capsule that protects its delicate inner structures.

If the kidney is bisected from top to bottom, the two major regions that can be visualized are the outer cortex and the inner region referred to as the medulla. The medulla is divided into multiple cone-shaped masses of tissue called renal pyramids. The base of each pyramid originates at the border between the cortex and medulla and terminates in the papilla, which projects into the space of the renal pelvis, a funnel-shaped continuation of the upper end of the urethra. The outer border of the pelvis is divided into open-ended pouches called major calyces that extend downward and divide into minor calyces, which collect urine from the tubules of each papilla. The walls of the calyces, pelvis, and urethra contain contractile elements that propel the urine toward the bladder, where urine is stored until it is emptied by micturition.\[42\]

\[42\] Text book of Medical Physiology 11\textsuperscript{th} edition 308-309.
Functions of kidney:

Renal Blood Supply:-

Blood flow to the two kidneys is normally about 22 per cent of the cardiac output, or 1100 ml/min. The renal artery enters the kidney through the hilum and then branches progressively to form the interlobular arteries, arcuate arteries, interlobular arteries (also called radial arteries) and afferent arterioles, which lead to the glomerular capillaries, where large amounts of fluid and solutes (except the plasma proteins) are filtered to begin urine formation (Figure 26 – 3). The distal ends of the capillaries of each glomerular coalesce to form the efferent arteriole, which leads to a second capillary network, tubular capillaries, that surrounds the renal tubules.

Excretion Of Metabolic Waste Products, Foreign Chemicals, Drugs, And Hormone Metabolites:-

The kidneys are the primary means for eliminating waste products of metabolism that are no longer needed by the body. These products include urea (from the metabolism of amino acids), creatinine (from muscle creatinine), uric acid (from nucleic acids), end products of hemoglobin breakdown (such as bilirubin), and metabolites of various hormones. These waste products must be eliminated from the body as rapidly as they are produced. The kidneys also eliminate most toxins and other foreign substances that are either produced by the body or ingested, such as pesticides, drugs, and food additives.

The Nephron is The Functional Unit of The Kidney:-

Each kidney in the human contains about 800,000 to 1 million nephrons, each capable of forming urine. The kidney cannot regenerate new nephrons. Therefore, with renal injury, disease, or normal aging, there is a gradual decrease in nephrons number. After age 40, the number of functioning nephrons usually decreases about 10 per cent every 10 years; thus, at age 80, many people have 40 per cent fewer functioning nephrons than they did at age 40. This loss is not life threatening because adaptive changes in the remaining
Nephrons allow them to excrete the proper amounts of water, electrolytes, and waste products.

**Micturition:-**

Micturition is the process by which the urinary bladder empties when it becomes filled. This involves two main steps; first, the bladder fills progressively until the tension in its walls rises above a threshold level; this elicits the second step, which is a nervous reflex called the micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate. Although the micturition reflex is an autonomic spinal cord reflex, it can also be inhibited or facilitated by centers in the cerebral cortex or brain stem.

**Facilitation or Inhibition of Micturition by the Brain:-**

The micturition reflex is a completely autonomic spinal cord reflex, but it can be inhibited or facilitated by centers in the brain. These centers include (1) strong facilitative and inhibitory centers in the brain stem, located mainly in the pons, and (2) several centers located in the cerebral cortex that are mainly inhibitory but can become excitatory.

The micturition reflex is the basic cause of micturition, but the higher centers normally exert final control of micturition as follows:

- The higher centers keep the micturition reflex partially inhibited, except when micturition is desired.
- The higher centers can prevent micturition, even if the micturition reflex occurs, by continual tonic contraction of the external bladder sphincter until a convenient time presents itself.
- When it is time to urinate, the cortical centers can facilitate the sacral micturation centers to help initiate a micturition reflex and at the same time inhibit the external urinary sphincter so that urination can occur.
Voluntary urination is usually initiated in the following way: First, a person voluntarily contracts his or her abdominal muscles, which increases the pressure in the bladder and allows extra urine to enter the bladder neck and posterior urethra under pressure, thus stretching their walls. This stimulates the stretch receptors, which excites the micturition reflex and simultaneously inhibits the external urethral sphincter. Ordinarily, all the urine will be emptied, with rarely more than 5 to 10 milliliters left in the bladder.43

Etiology and Epidemiology:-

<table>
<thead>
<tr>
<th>TABLE 2 : Population at Risk for CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65</td>
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<tr>
<td>Diabetes type 1 and 2</td>
</tr>
<tr>
<td>Family history of renal disease</td>
</tr>
<tr>
<td>Autoimmune disease</td>
</tr>
<tr>
<td>Systemic infections</td>
</tr>
<tr>
<td>Urinary tract infections/ stones</td>
</tr>
<tr>
<td>Urinary tract obstructions</td>
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<tr>
<td>Recovery of acute kidney injury</td>
</tr>
<tr>
<td>Hypertensive’s</td>
</tr>
<tr>
<td>Drug abusers: Non-steroidal anti inflammatory drugs (NSAIDs), analgesics/ heroin</td>
</tr>
<tr>
<td>Neoplasia</td>
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<tr>
<td>Low birth weight</td>
</tr>
<tr>
<td>Reduced kidney mass</td>
</tr>
<tr>
<td>Low income</td>
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<tr>
<td>Low education</td>
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</tbody>
</table>

*Perhaps, an appropriate name for this group of patients would be CKD stage ‘0’.

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The most frequent cause of CKD is diabetic nephropathy, most often secondary to type 2 diabetes mellitus. Hypertensive nephropathy is a common cause of CKD in the elderly, in whom chronic renal ischemia as a result of small and large vascular disease may be under recognized. Progressive nephrosclerosis from vascular disease is the renal correlate of the same processes that lead to coronary heart disease and cerebrovascular disease. The increasing incidence of CKD in the elderly has been ascribed, in part, to decreased mortality from the cardiac and cerebral complications of atherosclerotic vascular disease in these individuals, enabling a greater segment of the population to manifest the renal component of generalized vascular disease. Nevertheless, it should be appreciated that overwhelmingly the vast majority of those with early stages of renal disease, especially of vascular origin, will succumb to the cardiovascular and cerebrovascular consequences of the vascular disease before they can progress to the most advanced stages of CKD. The early stage of CKD, manifesting as albuminuria and even a minor decrement in GFR, is now recognized as a major risk factor for cardiovascular disease.

The striking interindividual variability in the rate of progression to CKD has an important heritable component, and a number of genetic loci that contribute to the progression of CKD have been identified. Similarly, it has been noted that women of reproductive age are relatively protected against progression of many renal diseases, and sex-specific responses to angiotensin II and its blockade have been identified.44

**Pathophysiology of CKD:**

Chronic Kidney disease is any illness that has existed for > 3 months with either kidney damage or low GFR. Kidney damage manifests as abnormal gross or histopathological abnormality or investigation reveal urinary abnormality, biochemical abnormality & imaging abnormality indicating kidney dysfunction.

**Pathophysiology of Chronic Kidney Disease:**

The Pathophysiology of CKD involves two broad sets of mechanisms of damage:

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(1) Initiating mechanisms specific to the underlying etiology (e.g., immune complexes and mediators of inflammation in certain types of glomerular nephritis, or toxin exposure in certain diseases of the renal tubules and interstitium).^{45}

- Immune mechanism
- Inflammation
- Toxins

(2) A set of progressive mechanisms, involving hyper filtration and hypertrophy of the remaining viable nephrons, that are a common consequence following long-term reduction of renal mass, irrespective of underlying etiology. The responses to reduction in nephrons number are mediated by vasoactive hormones, cytokines, and growth factors. Eventually, these short-term adaptations of hypertrophy and hyper filtration become maladaptive as the increased pressure and flow predisposes to sclerosis and dropout of the remaining nephrons. Increased interregnal activity of the rennin-angiotensin axis appears to contribute both to the initial adaptive hyper filtration and to the subsequent maladaptive hypertrophy and sclerosis, the latter, in part, owing to the stimulation of transforming growth factor β (TGF-β). This process explains why a reduction in renal mass from an isolated insult may lead to a progressive decline in renal function over many years.^{46}

**The Stages of CKD and Identification of At-Risk Populations:**

It is important to identify factors that increase the risk for CKD, even in individuals with normal GFR.

**Risk factors**

Hypertension, Diabetes mellitus, autoimmune disease,

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^{45} Harrison’s internal medicine 17th edition II, 1762.

Older age, African ancestry, a family history of renal disease, h/o Acute Renal Failure, presence of proteinuria, abnormal urinary sediment, or structural abnormalities of the urinary tract.

**Etiopathogenesis:-**

All chronic nephropathies can lead to CRF. The diseases leading to CRF can generally be classified into two major groups: those causing glomerular pathology, and that causing tubulointerstitial pathology. Though this classification is useful to facilitate study, the disease rarely remains confined to either glomerular or tubulointerstitial tissue alone. In the final stage of CRF, all parts of the nephrons are involved.

**Diseases causing glomerular pathology:-**

A number of glomerular diseases associated with CRF have their pathogenesis in immune mechanisms (page 685). Glomerular destruction results in changes in filtration process and leads to development of the nephritic syndrome characterized by proteinuria, hypoalbuminaemia and edema. The important examples of chronic glomerular diseases causing CRF are covered under two headings: primary and systemic.

I. Primary glomerular pathology

II. Systemic glomerular pathology

**Diseases causing tubulointerstitial pathology:**

Damage to tubulointerstitial tissues results in alterations in reabsorption and secretion of important constituent’s leads to excretion of large volumes of dilute urine. Tubulointerstitial diseases can be categorized according to initiating etiology into 4 groups: vascular, infections, toxic and obstructive.
I. Vascular causes: Long-standing primary or essential hypertension produces characteristic changes in renal arteries and arterioles referred to as nephrosclerosis. Nephrosclerosis causes progressive renal vascular occlusion terminating in ischemia and necrosis of renal tissue.

II. Infections causes: A good example of chronic renal infection causing CRF is chronic pyelonephritis. The chronicity of process results in progressive damage to increasing number of nephrons leading to CRF.

III. Toxic causes: Some toxic substances induce slow tubular injury, eventually culminating in CRF. The most common example is intake of high doses of analgesics such as phenacetin, aspirin and acetaminophen (chronic analgesic nephritis). Other substances that can cause CRF after prolonged exposure are lead, cadmium and uranium.

IV. Obstructive causes: Chronic obstruction in the urinary tract leads to progressive damage to the nephrons due to fluid back-pressure. The examples of this type of chronic injury are stones, blood clots, tumors, strictures and enlarged prostate.

Pathophysiology and Biochemistry of Uremia:-

Although serum urea and creatinine concentrations are used to measure the excretory capacity of the kidneys, accumulation of these two molecules themselves do not account for the many symptoms and signs that characterize the uremic syndrome in advanced renal failure. Hundreds of toxins that accumulate in renal failure have been implicated in the uremic syndrome. These include water-soluble, hydrophobic, protein-bound, charged, and uncharged compounds. Additional categories of nitrogenous excretory products include guanido compounds, urates and Hippocrates, products of nucleic acid metabolism, polyamines, myoinositol, phenols, benzoates, and in doles. Compounds with a molecular mass between 500 and 1500 Da, the so-called middle molecules, are also retained and contribute to morbidity and mortality. It is thus evident that the plasma concentrations of urea and creatinine should be viewed as being readily measured, but incomplete, surrogate markers for
these compounds and monitoring the levels of urea and creatinine in the patient with impaired kidney function represents a vast over-simplification of the uremic state.

<table>
<thead>
<tr>
<th>Uremic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water-soluble, hydrophobic, protein-bound, charged, and uncharged compound</td>
</tr>
<tr>
<td>Nitrogenous excretory</td>
</tr>
<tr>
<td>Compounds, urates and Hippocrates, products of nucleic acid metabolism, polyamines</td>
</tr>
<tr>
<td>Myoinositol, phenols, benzoates, and in doles</td>
</tr>
<tr>
<td>Urea and creatinine</td>
</tr>
</tbody>
</table>

**Flow Chart No 2: Pathophysiology and Biochemistry of Uremia**

The uremic syndrome and the disease state associated with advanced renal impairment involve more than renal excretory failure. A host of metabolic and endocrine functions normally undertaken by the kidneys are also impaired, and this results in Anemia, malnutrition, and abnormal metabolism of carbohydrates, fats, and proteins. Furthermore, plasma levels of many hormones, including PTH, insulin, glucagon, sex hormones, and prolactin, change with renal failure as a result of urinary retention, decreased degradation, or abnormal regulation. Finally, progressive renal impairment is associated with worsening systemic inflammation. Elevated levels of C-reactive protein are detected along with other acute-phase reactants, while levels of so-called negative acute-phase reactants, such as albumin and fetuin, decline with progressive renal impairment. Thus, renal impairment is important in the malnutrition-inflammation-atherosclerosis/ calcification syndrome, which contributes in turn to the acceleration of vascular disease and co morbidity associated with advanced renal disease.
Disturbance in metabolic and endocrinial functions
→
Anemia & Malnourishment →
Abnormal metabolism →
Carbohydrate, fats, proteins →
Abnormal levels hormone →
PTH, Insulin, Glucagon, Sex hormone, prolactin →
Renal failure result →
Urinary retention, decreased degradation, →
Inflammation →
Atherosclerosis/ calcification →
Acceleration of vascular disease

Flow Chart No 3: Pathophysiology and Biochemistry of Uremia

In summary, the path physiology of the uremic syndrome can be divided into manifestations in three spheres of dysfunction:

1) Those consequent to the accumulation of toxins normally undergoing renal excretion, including products of protein metabolism.
2) Those consequent to the loss of other renal functions, such as fluid and electrolyte homeostasis and hormone regulation.
3) Progressive systemic inflammation and its vascular and nutritional consequences.

Chronic Kidney Disease:

Chronic kidney disease (CKD) encompasses a spectrum of different path physiologic processes associated with abnormal kidney function, progressive decline in glomerular filtration rate (GFR). Table 1-1 provides a widely accepted classification, based on recent guidelines of the National Kidney foundation (Kidney Dialysis Outcomes Quality Initiative (KDOQI), in which stages of CKD are defined according to the estimated GFR.
The term chronic renal failure applies to the process of continuing significant irreversible reduction in nephrons number, and typically corresponds to CKD stages 3-5. The path physiologic processes and adaptations associated with chronic renal failure will be with the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys results in the uremic syndrome. This syndrome leads to death unless the toxins are removed by renal replacement therapy, using dialysis or kidney transplantation.

**TABLE 1-1 CLASSIFICATION OF CHRONIC KIDNEY DISEASE (CKD)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR, ml/min per 1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;90&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>≥ 90&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

<sup>a</sup> with risk factors for CKD (see text)  
<sup>b</sup> with demonstrated kidney damage (e.g. persistent proteinuria, abnormal urine sediment, abnormal blood and urine chemistry, abnormal imaging studies).

**Note:** GFR, Glomerular filtration rate.


**GFR Estimation:**

Two equations commonly used to estimate GFR are shown in Table1-2 and incorporate the measured plasma creatinine concentration, age, sex, and ethnic origin reporting of estimated GFR, or “e-GFR,” using one of these equations.

<sup>47</sup> NKF KDOQI GUIDELINES
Table 1-2

**Recommended equations for Estimation of Glomerular Filtration Rate (GFR) Using Serum Creatinine Concentration (Pcr), Age, Sex, Race and Body Weight**

1. Equation from the Modification of Diet in Renal Disease study$^a$
   
   Estimated GFR (mL/min per 1.73m$^2$) = 1.86 X (Pcr)$^{-1.154}$ X (age)$^{-0.203}$
   
   Multiply by 0.742 for women
   
   Multiply by 1.21 for African Americans

2. Cockcroft-Gault equation
   
   Estimated Creatinine Clearance (mL/min)
   
   (140 – Age X body weight, kg)
   
   =------------------------------------------
   
   72 X Pcr (mg/dL)
   
   Multiply by 0.85 for women

$^a$ Equation is available in hand-held calculators and in tabular form.


**GFR with Age and Creatinine level:**

The normal annual mean decline in GFR with age from the peak GFR (~120mL/min per 1.73m$^2$) attained during the third decade of life is ~ 1 mL/min per year per 1.73m$^2$, reaching a mean value of 70mL/min per 1.73m$^2$ at age 70. The mean GFR is lower in women than in men. For example, a woman in her 80s with a normal serum creatinine may have a GFR of just 50mL/min per 1.73m$^2$. Thus, even a mild elevation in serum creatinine concentration (e.g. 130 µmol/L (1.5mg/dL)), often signifies a substantial reduction in GFR in most individuals.

**Mechanisms:-**

**Raised intra- glomerular pressure:**

- As nephrons scar and ‘drop out,’ remaining nephrons undergo compensatory adaptation, with blood flow per nephrons attempting to ‘normalize’ GFR (the Brenner Hypothesis).
- Glomerular capillary wall permeability is a feature of glomerular diseases.
- Renal vasodilatation may be an initiating event, with the glomerular exposed to a higher capillary pressure.

**Glomerular damage:**

- Intra glomerular pressure -> wall stress and endothelial injury.
- Strain on mesangial cells -> matrix deposition mediated (in part) by angiotensin II and cytokine release (TGF – β, PDGF).

**Proteinuria:** - May be due to an underlying glomerular lesion, or result from raised intra glomerular pressure. Protein or factors bound to filtered albumin (such as fatty acids, growth factors or metabolic end-products) may lead to:

- Direct proximal tubular cell injury.
- Local cytokine synthesis (⇒ recruitment of interstitial inflammatory cells).
- Pro-fibrotic factors ⇒ interstitial scarring.
- Trans- differentiation of tubular cells into fibroblasts.

**Tubulointerstitial scarring:** - The degree of tubulointerstitial damage correlates better with long-term prognosis than glomerular damage. Proteinuria may itself be harmful to the tubulointerstitial, but chronic ischemic damage is also important: tissue oxygen tension is relatively low in the renal medulla, making tubules sensitive to hypoxic injury. Chronic ischemia occurs with:

- Damage to glomerular capillaries (glomerular sclerosis ⇒ altered per tubular perfusion).
- RAS activation ⇒ interregnal vasoconstriction.
- Intra tubular capillary loss and increased diffusion distance between capillaries and tubular cells, leads to vicious cycle of hypoxic.

**Significance of Albuminuria, Proteinuria, Microalbumuria:**

Measurement of albuminuria is also helpful for monitoring nephrons injury and the response to therapy in many forms of CKD, especially chronic glomerular diseases. While an accurate 24-h urine collection is the “gold standard”
for measurement of albuminuria, the measurement of albumin-to-creatinine ratio in a spot first-morning urine sample is often more practical to obtain and correlates well, but not perfectly, with 24-h urine collections. Persistence in the urine of >17 mg of albumin per gram of creatinine in adult males and 25 mg albumin per gram of creatinine in adult females usually signifies chronic renal damage. Microalbuminuria refers to the excretion of amounts of albumin too small to detect by urinary dipstick or conventional measures of urine protein. It is a good screening test for early detection of renal disease, in particular, and may be a marker for the presence of microvascular disease in general. If a patient has a large amount of excreted albumin, there is no reason to perform an assay for microalbuminuria.

**Progression of Diseases:**

**Stages 1 & 2 CKD:**

- Decreased GFR
- Renal parenchymal disease
- Poly cystic disease
- Glomerular nephritis
- Paranechymal and vascular diseases.
- Well preserved GFR.

The usually are not associated with any symptoms arising from the decrement in GFR. However, there may be symptoms from the underlying renal disease itself, such as edema in patients with nephritic syndrome or signs of hypertension secondary to the renal parenchymal disease in patients with polycystic kidney disease, some forms of glomerular nephritis, and many other parenchymal and vascular renal diseases, even with well-preserved GFR.

**GFR progresses to stages 3 & 4:**

- Organs affected
- Anemia
- Associated
- easy fatigability; decreasing appetite with progressive malnutrition
• Abnormality
• calcium, phosphorus, mineral regulating hormone, Parathyroid hormone
• sodium, potassium, water, and acid-base homeostasis

If the decline in GFR progresses to stages 3 & 4, clinical and laboratory complications of CKD become more prominent. Virtually all organ systems are affected, but the most evident complications include Anemia and associated easy fatigability; decreasing appetite with progressive malnutrition, abnormalities in calcium, phosphorus, and mineral – regulating hormones, such as 1,25 (OH)₂ D₃ (calcitriol) and parathyroid bromine (PTH); and abnormalities in sodium, potassium, water, and acid-base homeostasis.

Progresses to stage 5 CKD:

• Disturbance
• Nutritional status
• Water and electrolyte homeostasis

If the patient progresses to stage 5 CKD, toxins accumulate such that patients usually experience a marked disturbance in their activities of daily living, well-being, nutritional status, and water and electrolyte homeostasis, eventuating in the uremic syndrome. This state will culminate in death unless renal replacement therapy (dialysis or transplantation) is instituted.

CKD & Other disease (Anemia, Hypertension & diabetes)

Anemia of CKD

Erythropoietin (EPO) and the kidney:-

Red blood cell production is tightly regulated by a number of different growth factors. EPO is essential for the terminal maturation of erythrocytes, and differs from other growth factors in that it is produced by per tubular interstitial fibroblasts in the outer renal medulla and deep cortex of the kidney rather than the bone marrow. The kidney is ideally placed to regulate RBC production, as it is
uniquely able to sense and control both $O_2$ tension and circulating volume (and differentiate between the two):

- Red cell mass is regulated by EPO.
- Circulating volume is regulated by salt and water excretion.
- The kidney maintains the haematocrit at 45% in normal conditions. (maximizing tissue $O_2$ delivery)

Chronic kidney disease, renal scarring → ↓ EPO synthesis, ↓ RBC production and anemia this occurs in most form of advanced CKD (e GFR < 35 mL/min), with a few exceptions:

- Adult polycystic kidney disease.
- Benign renal cysts.
- Renal cell carcinoma.

In these instances, EPO may be overproduced.

**Differential diagnosis of anemia in CKD patients:**

EPO deficiency is not the only cause of ↓ Hb in CKD

Patients with CKD are susceptible to all other causes of anemia, so these should be actively sought in patients who appear disproportionately anemic or EPO resistant:

- Iron deficiency.
- Blood loss (GI tract, haemodialysis)
- Folate deficiency
- B12 deficiency
- Haemolysis
- Myelodysplasia
- Myeloma
Hypertension

Hypertension is the second leading cause of end-stage renal disease (ESRD). As an example, according to the United States Renal Data System (U. S. Renal Data System, 2009), about 51 -63% of all patients with CKD are hypertensive. This number grows to 90% in patients over 65 years. In the corresponding general population the incidence of hypertension is 11 – 13% and 50%, respectively.

Hypertension causes a nephrosclerotic glomerulopathy characterized by

i. Renal vasculopathy affecting pre glomerular arteries and arterioles, resulting mainly from atherosclerosis, endothelial dysfunction, wall thickening and fibrosis.

ii. Microvascular disease of the glomerular tuft capillaries.

iii. Diffuse glomerular sclerosis and, less often, focal and segmental glomerular sclerosis (FSGS), involving damage to the filtration barrier constituents (Podocytes, mesangial cells and basement membranes.

iv. Interstitial fibrosis (Rosario & Wesson, 2006). Overall renal blood flow decreases as a consequence of arteriolar vasculopathy, vascular obstruction and decrease vascular density. However, GFR initially stays relatively constant. This is due to (i) increased glomerular capillary pressure resulting from deficient or upwardly reset renal auto regulation; and (ii) damage to the filtration barrier resulting in greater permeability. Subsequently, GFR decreases as a consequence of a progressive loss of surface area, mesangial hypertrophy and increasing glomerular and per tubular fibrosis. Concomitantly, basement membrane alterations produce albuminuria and protein hyper filtration.
| Renal vasculopathy                      | Pre glomerular arteries and arterioles affected ▼  
|                                         | Endothelial dysfunction ▼  
| Micro vascular Disease                  | Wall thickening and fibrosis ▼  
| Filtration barrier damage               | Glomerular tuft capillaries ▼  
| Interstitial fibrosis                   | Podocytes mesangial cells and basement membrane ▼  
| GFR decreased                           | Arteriolar vasculopathy, vascular obstruction, depressed vascular density ▼  
| Alteration basement                     | loss of surface area, mesangial hypertrophy, increasing glomerular and per tubular fibrosis ▼  
|                                        | proteinuria and alununria ▼  

**Flow Chart No. 4: Hypertension causes a nephrosclerotic glomerulopathy characterized**

**Hypertension – associated CKD progression is highly dependent on**

(i) Renal blood flow auto regulation and renal hemodynamic.

(ii) Artificial maneuvers or genetically-determined factors that modify renal function or renal tissue homeostasis, independently of their action on blood pressure or renal hemodynamic.

(iii) Genetic susceptibility factors. Renal auto regulation endows the kidneys with the capacity to maintain constant glomerular flow and pressure upon changes in systemic and renal perfusion pressure. Auto regulation is attained through vasoconstriction and vasodilatation of pre glomerular (afferent) arteries and arterioles. In addition to the insulation of renal function from the influence of fluctuations in systemic blood pressure, one of the most important physiological functions of auto regulation is believed to be the protection of renal tissues from mechanical overload derived from high blood pressure.48

48 Pharmacology & Therapeutics, Common path physiological mechanisms of chronic kidney disease: therapeutic perspective.
Diabetic nephropathy:

The diabetic nephropathy is leading cause of ESRD in the USA and Europe (Molitch et al., 2004). In fact, about 50% of ESRD patients (in the USA) are diabetic (U.S.Renal Data System, 2009). It is important to consider that hyperglycemia is primary initiator of diabetic nephropathy. In the absence of elevated glycemic, nephropathy does not develop. However, diabetic nephropathy holds a genetic component at two levels: first, the elevation of glycemic; and second, at establishing a genetic back-ground where nephropathy can occur (in the presence of hyperglycemia). Only 30% of patients with type 1, and 35 – 40% of patients with type 2 diabetes develop diabetic nephropathy irrespective of glycemic control (Diabetes Control & Complications, 1995). The clinical history of a typical patient starts with symptoms of hyper filtration (elevated values of GFR) and occasional microalbuminuria, which may last approximately 5 years. During the next – 20 years, microalbuminuria turns into progressively higher proteinuria, whereas GFR declines. Finally, the patient undergoes renal insufficiency with severe proteinuria, which eventually evolves towards ESRD (Schena & Gesualdo, 2005).

Diabetes patients

- Type1-30%
- Type2-35-40%
- Hyper filtration (elevated values of GFR) 5years
Diagnosing CKD:

Always assume a GFR represents acute renal failure until proven otherwise. If uncertain, repeat within 5 days and refer as necessary.

<table>
<thead>
<tr>
<th>TABLE 10: Manifestations Attributable to Uraemic Toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
</tr>
<tr>
<td>- Atheromatosis</td>
</tr>
<tr>
<td>- Arteriosclerosis</td>
</tr>
<tr>
<td>- Cardiomyopathy</td>
</tr>
<tr>
<td>- Decreased diastolic compliance</td>
</tr>
<tr>
<td>Nervous system</td>
</tr>
<tr>
<td>- Concentration disturbances</td>
</tr>
<tr>
<td>- Cramps</td>
</tr>
<tr>
<td>- Dementia</td>
</tr>
<tr>
<td>- Depression</td>
</tr>
<tr>
<td>- Fatigue</td>
</tr>
<tr>
<td>- Headache</td>
</tr>
<tr>
<td>- Seizures</td>
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<tr>
<td>- Asterix (flaps)</td>
</tr>
<tr>
<td>- Motor weakness</td>
</tr>
<tr>
<td>- Polyneuritis</td>
</tr>
<tr>
<td>- Reduced sociability</td>
</tr>
<tr>
<td>- Restless legs</td>
</tr>
<tr>
<td>- Sleep disorders</td>
</tr>
<tr>
<td>- Stupor, coma</td>
</tr>
<tr>
<td>Haematological system</td>
</tr>
<tr>
<td>- Bleeding</td>
</tr>
<tr>
<td>- Hypercoagulability</td>
</tr>
<tr>
<td>Immunological system</td>
</tr>
<tr>
<td>- Inadequate antibody formation</td>
</tr>
<tr>
<td>- Stimulation of inflammation</td>
</tr>
<tr>
<td>- Susceptibility of cancer</td>
</tr>
<tr>
<td>- Susceptibility of infection</td>
</tr>
<tr>
<td>Endocrinology</td>
</tr>
<tr>
<td>- Dyslipidaemia</td>
</tr>
<tr>
<td>- Glucose tolerance</td>
</tr>
<tr>
<td>- Growth retardation</td>
</tr>
<tr>
<td>- Hyperparathyroidism</td>
</tr>
<tr>
<td>- Impotence, diminished libido</td>
</tr>
<tr>
<td>Bone disease</td>
</tr>
<tr>
<td>- Adynamic bone disease</td>
</tr>
<tr>
<td>- Amyloidosis</td>
</tr>
<tr>
<td>- Osteitis fibrosa</td>
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<tr>
<td>- Osteomalacia</td>
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<td>- Osteoporosis</td>
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<td>Skin</td>
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<td>- Melanosis</td>
</tr>
<tr>
<td>- Pruritus</td>
</tr>
<tr>
<td>- Uraemia frost</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
</tr>
<tr>
<td>- Anorexia</td>
</tr>
<tr>
<td>- Dyspepsia</td>
</tr>
<tr>
<td>- Hiccups</td>
</tr>
<tr>
<td>- Nausea, vomiting</td>
</tr>
<tr>
<td>- Pancreatitis</td>
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<td>- Sleep apnoea syndrome</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>- Hypothermia</td>
</tr>
<tr>
<td>- Thirst</td>
</tr>
<tr>
<td>- Uraemic foetor</td>
</tr>
<tr>
<td>- Weight loss</td>
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</tbody>
</table>