PROGRESSIVE RENAL DYSFUNCTION OF IRAQI PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD) IS ASSOCIATED WITH FAMILY HISTORY, CREATININE, GFR AND HYPERTENSION.

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Background and objectives: This study was designed to examine the clinical diagnostic characteristics of family members affected with Autosomal dominant polycystic kidney disease (ADPKD) in Iraq.

Materials and methods: Thirty two families with 61 individuals affected with ADPKD, and 35 control healthy individuals were used to examine the abdominal features by ultrasound, serum levels of creatinine, urea and GFR together with blood pressure (BP) and lipid profile to assign the stages of disease. Statistical analyses was done by using t-test, chi-square, or ANOVA.

Results: The development of multiple cysts and massive enlargement of kidneys size were clearly noted at 40 years of age. These changes were associated at different magnitudes with family history, disease and age progression of nearly all patients. As disease progresses, a significant increase in the levels of both of creatinine and urea (p<0.05), but a decrease in GFR. Similarly, hypertension was found in a 36% of ADPKD patients (p<0.05), and HDL (but no others) was significantly differed (p>0.05) compared to controls.

Conclusion: Results indicate that multiple factors such as creatinine, urea, GFR, and hypertension as well as family history, and HDL were clearly seen to be associated with disease progression rather than the onset of the ADPKD. It suggests that multiple determinants/markers may contribute to disease progression including the genetic heterogeneity/polymorphism of PKD.

Introduction: Polycystic kidney diseases (PKD) are a group of developmental renal disorders that are characterized by progressive fluid accumulation in dilated renal tubules to form cysts, generating kidney enlargement and numerous large cysts which eventually lead to renal failure (Bisceglia et al., 2006). Three forms of PKD with the autosomal dominant polycystic kidney disease (ADPKD) is being the most common (85%) and a delayed in showing symptoms; autosomal recessive PKD (ARPKD) usually lethal at birth but is less common (15%); and the lethal syndrome represented by Meckel syndrome that encompass central
nervous system and digital defects (Harris, 2009). Most of ADPKD manifestations are directly related to the development and enlargement of renal cysts, although in most patients’ renal function preserved within the normal range, in spite of relentless growth of cysts. However, only 5% of people at the age of 60 years live without suffering from ESRD (Grantham, 2008; Takiar and Caplan, 2011). This condition can contribute to glomerular hyper filtration seen in children and young adults (Wong et al., 2004; Nagao et al., 2006). Hypertension is the most common manifestation of ADPKD and it may develop at early age (34.8 years age in PKD1 patients vs. 49.7 years age in PKD2 patients years) (Boucher and Sandford, 2004). Blood pressure (Bp>140/90 mm Hg) existing in around 50% of patients aged 20–34 years with ADPKD even before there is any decrease in kidney function, which increases later to nearly 100% of patients with ESRD (Kelleher et al., 2004). In addition, ADPKD is an important risk factor for cardiovascular morbidity and mortality (Schrier, 2011; Katukuri et al., 2014). Extra renal cysts may arise in several organs such as liver (high), seminal vesicles (40%), pancreas (5%) and arachnoid membrane (8%) of ADPKD patients (Torra et al., 2008).

New diagnostic criteria were established for PKD1 in patients at risk from 15 to 59 years of age, although it did not do well when applied to patients with PKD2 that reduced the test sensitivity (Pei et al., 2009). In the case of the younger age where ultrasound diagnosis is not accurate by giving uncertain results, a negative magnetic resonance imaging (MRI) or computed tomography is more effective with a higher resolution than that of ultrasound (Pei and Watnick, 2010). Alternatively, genetic diagnosis is more accurate test especially for patients at high risk younger than 30 years age. Genetic diagnosis in the case ADPKD is complex due to genetic heterogeneity with two causative gene PKD1 and PKD2 gene (Rossetti et al., 2007; Garcia-Gonzalez et al., 2007; Barua et al., 2009).

This study is planned to examine the clinical, biochemical, hypertension with its relevant risk factors characteristics of ADPKD in local patients aiming to correlate these criteria with other factors such as age, gender family history with disease progression.

Materials and Methods:-

Samples and subjects
A total of 61 individuals from 32 families with ADPKD presented in dialysis centers of six teaching hospitals in Baghdad city, together with an additional 35 control healthy individuals (with no history of ADPKA) were recruited in this study. Out of those patients, there were 33 females and 28 males with an age range of 7–65 years. All patients had some sort of renal failure with varying degrees based on clinical and physical examination and family history generated by hospital record. This information was further examined by using information of the informed consent and personal interview of all individuals used in this study.

Clinical Examination:-
Abdominal ultrasound examination was performed by a radiologist for all cases with ADPKD except healthy control subjects. Diagnosis of ADPKD was made according to unified criteria for the ultrasonographic diagnosis of ADPKD (Pei et al., 2009), and with patients having appositive family history of ADPKD (Barua et al., 2009).

Blood Pressure:-
Blood pressure is generally measured by an indirect method, using a mercury sphygmomanometer. The subjects were classified as hypertensive if systolic blood pressure was equal or more than 169 mmHg or diastolic blood pressure equal or more than 95 mmHg or if they were on antihypertensive medication according to criteria of 1993 guidelines for the management of mild hypertension WHO/ISH (International Society of Hypertension) (Zanchetti et al., 1993).

Biochemical Testing:-
Blood samples from all these individual were used for testing biochemical and metabolic parameters, including the total concentration of urea, creatinine, triglycerides, total cholesterol, high density lipoprotein (HDL-C) and albumin in serum by enzymatic method using a commercially available kits (HUMAN, Germany). The very low density lipoprotein (VLDL) and low density lipoprotein (LDL-C) were determined according to the conventional equation (Friedewald et al., 1978). Calculation of the
GFR by using the CKD-EPI Creatinine equation (Levey et al., 2009) to assign the stages of disease up to the definite chronic renal failure (CRF). This can be done at (https://www.kidney.org/apps/professionals/egfr-calculator), which allows estimation of GFR by simple software programs (eGFR).

Statistical Analysis:-
Data obtained (age and values of biochemical parameters) were expressed as means ± standard deviations, other data (gender, family history and hypertension) were expressed as a ratio with number. The comparison of continuous values between two groups was performed by using student t-test, whereas Chi square (c2) was used to compare non-continuous values. Differences in biochemical values were compared among study groups using one-way analysis of variance (ANOVA). p < 0.05 was set as statistically significant. All analyses were performed with the Statistical Package of Social Sciences (SPSS) software.

Results:-
Age, gender, family history, and blood pressure of ADPKD patients:-
Results obtained from a questionnaire containing age, gender at presentation, family history, and blood pressure measurement at the time of diagnosis were summarized in Table (1). Individuals of both patients and control groups did not differ significantly by age (p>0.05, t-test). The mean age of individuals with ADPKD was (32.89±15.7) ranging from 7 to 65 years and (31.17±13.8) for the control apparently healthy individuals ranging from 8 to 60 years. Among the ADPKD patients; there were 28/61 (45.9%) males and 33/61 (54.1%) females with no significant difference (p>0.05). A positive family history of renal disease was presented in 29/32 (90.6%, p<0.05) cases, and only 10.4% were with a negative family history. Hypertension was seen in 22/61 (36.1%, p<0.05) of ADPKD patients. Taken together, the results showed minor differences in respects to age, but slightly significant for gender and highly significant for family history and hypertension in the affected individuals with ADPKD in Iraq.

Table 1:- General characteristics of age, gender, family history and blood pressure of 61 ADPKD patients and 35 controls of apparently healthy individuals recruited in this study.

| Variables                                      | ADPKD patients (Mean ±SD) | Control Healthy (Mean ±SD) | P-Value |
|------------------------------------------------|---------------------------|-----------------------------|---------|
| Age (Range)                                    | (7-65)                    | (8-60)                      | 0.224   |
| Gender                                        | Male (54.1%)              | 25 (71.4%)                  | 0.199   |
|                                               | Female (45.9%)            | 10 (28.6%)                  |         |
| Blood pressure                                 | Hypertension (36.1%)      | 0                           | 0.001†† |
|                                               | Non-hypertensive (63.9%)  | 35(100%)                    |         |
| Family history                                 | Positive (90.6%)          | 0                           | 0.001*  |
|                                               | Negative (9.4%)           | 35(100%)                    |         |

Abbreviations: (*), significance at p<0.05; (††), values analyzed by Pearson Chi-square; (†††), values analyzed by (t-test).

Clinical Manifestations of ADPKD:-
The clinical features as tested by ultrasonography diagnostic criteria, state of renal function and the stages of renal disease were carried out and supervised by specialist renal consultant (Dr. Ali Al-Saeedi, Baghdad Central Medical City, College of Medicine, University of Baghdad). The ultrasound examination of kidneys patients showed a few small cysts with normal kidney size ranged between 9.4*4.0 cm to 10.6*4.6 cm (length*width) at an age younger than 30 years. Numerous multiple cysts of variable sizes were observed with a simple inflation in kidney size ranged between 12.9*4.8 cm to 15.9*6 cm (length*width) at an age ranged between 30 and 40 years. Numerous multiple cysts of variable sizes were seen in enlarged kidney size of approximately 18.8*8.6 cm (length*width) at an age above 40 years old. On the other hand, there were ten cases of the affected individuals with ADPKD had no cyst development within an age ranged between 7 and 32 years. In addition, there were three cases at an age ranged between 30 and 40 years who had a massive kidney enlargement with multiple cysts (the largest was about 10 cm*10 cm in diameter of both kidneys), (Figure 1). Those also had multiple small stones at both kidneys, chronic abdominal pain, weight loss and macroscopic hematuria. These cases are usually categorized as a giant polycystic kidney disease that were rarely occurred and accompanied by
severe symptoms leading to renal failure at early age. In all these cases, other organs like liver, pancreas, spleen, and ovaries had no cyst developed and were not affected by the disease.

**Figure 1:** Abdominal ultrasonography image for a 40 year old patient with ADPKD showing remarkably enlarged kidneys’ size with multiple cysts. The largest cysts was on the right kidney with 10*10cm in diameter (A) and the largest cysts was on the left kidney with 6.3*5.3cm in diameter (B).

**Serum Urea, Creatinine and GFR associated with disease stage:**
Laboratory testing of serum urea, serum creatinine and glomerular filtration rate (GFR) associated with ADPKD were estimated and when compared with those of the control group, by using ANOVA test, were found to be highly significant (p<0.05, for all) (Table 2). Importantly, the decline of serum urea and creatinine were progressively increased with age, but decreased progressively in age-dependent manner for GFR (Table 2). Therefore, the significant correlation of these parameters is only observed at age approximately more than 30 years old. For all values of the fourth, fifth, sixth and seventh patients’ age groups were highly significant for urea (p<0.05), similar significant pattern for creatinine (p<0.05), and was also consistently significant for GFR (p<0.05) (Table 2). This observation, on the contrary, was consistently within the normal range for all three parameters tested for the control group as well as for the early age groups 1, 2 and 3 of ADPKD patients (Table 2 legend).

**Table 2:** Biochemical characteristics of kidney function parameters (serum urea, serum creatinine and GFR values) for different age groups (1 to 7) of patients with ADPKD and control individuals and their association with disease stages.

| Variables | S. urea mg/dl | S. creatinine mg/dl | GFR# Values |
|-----------|---------------|---------------------|-------------|
| Age group (years) | no/ Total | Mean ± SD (range) | Mean ± SD (range) | Mean ± SD (range) | Disease Stage |
| 1 (6-14) | 10/61 | 31.27±8.96 (23.04-38.8) | 1.20±0.38 (0.84-1.75) | 99.33±40.2* (57-137) | Stage 1 (Normal/healthy) |
| 2 (15-23) | 10/61 | 40.29±13.35 (26.8-64.34) | 1.57±0.5 (0.84-2.28) | 62±24.39 (39-100) | Stage 2 (subclinical) |
| 3 (24-32) | 14/61 | 53.46±47.06 (15-165) | 1.75±0.64 (1.06-3.4) | 53±19.9 (35-97) | Stage 3 (subclinical) |
| 4 (33-41)* | 6/61 | 88.13±49.14* (49.19-163.8) | 4.36±2.1* (2.8-7.2) | 16.6±10.15* (7-35) | Stage 4 (CKD) |
| 5 (42-50)* | 12/61 | 142.34±79.6* (75-340.4) | 7.17±5* (3.01-20.2) | 10.9±5.83* (2-20) | Stage 5 (ESRD) |
| 6 (51-59)* | 6/61 | 188.54±69.17* (107.3-296) | 8.24±2.87* (5.017-11.16) | 6.33±3.35* (3-12) | |
| 7 (60-69)* | 3/61 | 214.29±24.89* (188.3-238) | 8.4±2.28* (6.8-11.05) | 6±2.64* (3-8) | |
| Control (8-60) | 35/35 | 33.84±7.2 (23.5-42.8) | 1.36±0.53 (0.48-2) | 67.8±33.32 (40-135) | Normal/healthy |
Abbreviations: S, Serum; GFR#, glomerular filtration rate mL/min per 1.73 m² that measured by the CKD-EPI creatinine equation (Levey et al., 2009); Significance at \( p<0.05 \); \( p-values \) of age groups 4, 5, 6, and 7 compared to the control group were as follows: \( (p=0.042, 0.000, 0.000, 0.000, \text{respectively}) \) for s. urea, \( (p=0.033, 0.000, 0.000, 0.000 \text{respectively}) \) for s. creatinine, and \( (p=0.000, 0.000, 0.000 \text{and 0.000, respectively}) \) for GFR values; Stages of disease were determined according to the GFR criteria (19); CKD, chronic kidney disease; ESRD, end stage renal disease.

Correlation of Hypertension and Lipoprotein in ADPKD patients:
In this study, hypertension was noted in 22 (36.1%) patients with ADPKD including 13 (59.1%) males and 9 (40.1%) females. The age mean of hypertensive ADPKD patients was \( (40.6\pm12.75) \). This was significantly different than the age mean \( (28.94\pm15.74) \) of non-hypertensive patients \( (t-test) \) (Table 3).

Correlation between hypertension and other related factors (GFR, serum triglyceride, serum total cholesterol, serum high density lipoprotein (HDL), serum low density lipoprotein (LDL) and serum albumin) were analyzed for the three groups: the hypertensive, non-hypertensive state of ADPKD patients, and for the apparently healthy control individuals. In general, results showed that all factors studied were not significantly different when hypertensive was compared with non-hypertensive ADPKD patients and with controls which indicates no major role in disease progression. In the case of GFR, there was only a significant difference \( (p<0.05) \) seen between values of ADPKD patients and the healthy control individuals; but it was not significant \( (p>0.05) \) between the patients themselves whether they were hypertensive or non-hypertensive (Table3). Similarly, the values of serum high density lipoprotein (HDL) showed a significant difference between hypertensive, non-hypertensive \( (p<0.05) \) ADPKD patients and healthy controls; but again this result was not significant between hypertensive and non-hypertensive ADPKD patients \( p>0.05 \) (\( p=0.065 \) and 0.413, respectively) (Table 3). The values of the remaining factors of serum triglyceride, serum total cholesterol, serum low density lipoprotein (LDL) and serum albumin did not show a significant difference \( (p>0.05, \text{respectively}) \) among the three categories (Table 3).

Table 3: Correlation between lipoprotein levels in ADPKD patients with and without hypertension compared to apparently healthy controls.

| Parameters                  | Hypertensive No. (% 22/61 36.1%) | Non-hypertensive No. (% 39/61 63.9%) | Control group | P-value |
|-----------------------------|----------------------------------|-------------------------------------|----------------|---------|
| Gender                      | ♂ 13/22 (59.1%)                  | ♂ 17/39 (59.1%)                    | 25             | -       |
|                             | ♀ 9/22 (40.9%)                   | ♀ 22/39 (40.9%)                    |                |         |
| Age                         | 40.6±12.75                      | 28.94±15.74                       | 31.17±13.8     | 0.004*  |
|                             | (20-65)                         | (7-60)                             | (8-60)         | †       |
| GFR ml/min/ 1.73m²          | 31.65±36.35                     | 40±37.24                           | 67.8±33.32     | 0.046*  |
|                             | (4-119)                         | (2-137)                            | (4-135)        | ††      |
| Serum Triglycerides mg/dl   | 202±100.59                      | 156.3±57.05                       | 181±69.61      | 0.434   |
|                             | (104.7-448)                     | (54.4-234)                         | (90.3-277)     | ††      |
| Serum Total-cholesterol     | 157.94±54.32                    | 151.87±53.93                      | 130±21.15      | 0.355   |
| (mg/dl)                     | (89-242.7)                      | (92.3-275)                         | (108-149.9)    | ††      |
| Serum High density          | 72.49±30.47                     | 98.17±31                           | 61.7±31.5      | 0.045*  |
| lipoprotein (mg/dl)         | (54.9-133.4)                    | (60.2-160.9)                       | (15.5-128.8)   | ††      |
| Serum Low density lipoprotein (mg/dl) | 56.54±22.2     | 72.6±53.76                         | 42.97±28.68    | 0.23    |
|                             | (28.3-94.9)                     | (24.8-164.8)                       | (21.5-107.3)   | ††      |
| Serum albumin (g/dl)        | 4.7±0.55                        | 4.56±1.13                         | 5.1±0.82       | 0.278   |
|                             | (3.9-5.6)                       | (2.1-6)                           | (4.3-7)        | ††      |

Abbreviations: Significance at \( p<0.05 \); (†) statistical analysis done by t-test; (††)statistical analysis done by ANOVA test.
Discussion:-

For diagnostic purposes, as in this study and others, ultrasonographic imaging was used to determine the kidney size, with low accuracy (Arruda et al., 2011; Panizo et al., 2012). Although, MRI and CT has similar accuracy and reliability in determining cyst volume and non-cystic renal parenchyma, with the latter being faster but they are still considered expensive, not available in all hospitals and time consuming (Chapman and Wei, 2011). In this study, as the ultrasonographic images showed an increase in both kidneys’ and cysts’ sizes, it was also biochemically accompanied by a progressive increase in both urea and creatinine but a gradual decline in GFR values which all were progressively correlated with age progression (as defined by age grouping) and the significance of family history in local affected ADPKD patients. In addition, although, the decline in kidney function was not strictly correlated with age where it occurs after age of 30 years but it linked strongly with the rate of enlargement of kidneys and cysts’ size. This may be explained by the appearance of cysts in the nephron segments, which may damage the renal parenchyma leading to remarkably enlarged and distorted kidneys as patients progressing to ESRD with age (Torres et al., 2012). At this stage, the average GFR values descends at a rate of 4.4–5.9 ml/min/year and with a yearly average of 0–3 ml/min/1.73 m2 depending on the chronic kidney disease (CKD) stage (Higashihara et al., 2012). Therefore, the biochemical parameters particularly at the early stage of ADPKD where the values of GFR were near the normal range that made it potentially not good biomarker candidate for disease onset, if any (Meijer et al., 2010; Gulick et al., 2011; Thong and Ong, 2013). Accordingly, other reliable biomarker candidates for the early of the disease have to be examined.

The development of hypertension in ADPKD patients at an age as early as of 20 years with a decline in the GFR compared to normotensive, suggest that hypertension plays a role in the progression of the renal disease (see Table 3). It has been shown that the appearance and severity of hypertension are correlated with a more rapid declining of renal function (Higashihara et al., 2012; Bartosik et al., 2008). It has been suggested that high blood pressure may occur before renal impairment with an average age in the beginning of 30 years (Thong and Ong, 2013). Therefore, hypertension is more likely to be associated with older age patients and to a lesser extent with disease stage. Although a third of patients had hypertension in this study, confirming similar previous results in Iraq (Alsaedi et al., 2011) other studies showed in much higher frequencies such as 83% of ADPKD patients in France (Cornec-Le Gall et al., 2013), in 73% of patients with ADPKD in the Southern Brazil (Alves et al., 2014), and in 75.5% of ADPKD patients in China (Liu et al., 2015).

The unsettled results for the lipid profile may also increase the progression to renal diseases in the hypertensive patients (see Table 3) particularly HDL but no other risk factors were significantly involved. This lipid profile is still controversial where there was no significant difference in values of serum albumin, total cholesterol, LDL; but there was a highly significance difference between serum triglyceride of hypertensive and non-hypertensive patients with ADPKD (Kocyigit et al., 2014). On the other hand, there were no significant differences in level of haematocrit, calcium, phosphorous, HDL, cholesterol, and triglycerides in patients (Panizo et al., 2012).

The phenotypic characteristics of ADPKD are highly variable between patients and genetically heterogeneous in same family as well as between different families indicates the effect of various genetic and environmental factors (Torres et al., 2007). Previous cross-sectional and longitudinal studies reported different types of mutations in PKD1 and PKD2 at an age range of 30-35 years (Granatham et al., 2006; Harris et al., 2006; Rossetti et al., 2009; Woon et al., 2015). There are also other environmental factors shown to increase the risk for ESRD, such as high protein and low potassium diets might contribute to the increased renal size, serum urea nitrogen and fibrosis. Furthermore, cigarettes smoking, heavy use of analgesics might be further contribute to chronic kidney disease progression in some patients (Orth and Hallan, 2008).

In conclusion, the association of clinical, family history, biochemical, and hypertension criteria with advancing disease stages in local patients was strong and suggest their contribution to renal failure. Such correlation was not so strong and controversial at earlier/onset stage of ADPKD as that seen with the advanced stage which may reflect the influence of genetic variability. Therefore, serum creatinine and GFR can serve as good diagnostic/prognostic markers for disease progression together with the cyst and kidney size.
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