Long-term results of children diagnosed with idiopathic nephrotic syndrome; single center experience

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Abstract
Aim: The aim of this study was to determine the long-term results of children followed up with a diagnosis of nephrotic syndrome in a single center.

Material and Methods: The medical data of 33 patients aged between 6 months and 10 years who were diagnosed with idiopathic nephrotic syndrome in our center between January 2000 and December 2012 and followed up for a period of 2-12 years were reviewed (Gulhane Military Medical Academy Ethics committee, 07.11.2012/10).

Results: The mean age of disease onset was 3.2±2.04 years (range: 0.5-10 years) and the mean follow-up period was 6±3.4 years (range: 2-12 years). Thirteen (39.4%) of the study group (or the patients) were female and 20 (60.6%) were male. Twenty seven (1.8%) of the patients were sensitive to steroid and 6 (18.1%) were resistant to steroid. Four (12.1%) of the steroid-resistant patients had steroid-dependent nephrotic syndrome, 5 (15.2%) had frequently relapsing nephrotic syndrome and 18 (54.5%) had rarely relapsing nephrotic syndrome. Histopathological diagnoses of six patients who underwent biopsy because of resistance to steroid were as follows: focal segmental glomerulosclerosis (n=3), C1q nephropathy (n=1), diffuse mesangial proliferation (n=1) and membranous nephropathy (n=1). Fifteen (45.5%) patients entered into full remission and 2 (6%) patients developed chronic renal failure. Treatment complications including decreased bone mineral density in three patients (9%), short stature in 2 patients (6%) and cataract in 2 patients (6%) developed.

Conclusions: Children with nephrotic syndrome carry a risk in terms of short stature, osteoporosis, cataract and renal failure in the long-term follow-up. It was observed that our rates of response to steroid were similar to the literature and the most common histopathological diagnosis was focal segmental glomerulosclerosis in our patients who underwent biopsy because of resistance to steroid. It was thought that multi-center studies should be conducted to demonstrate regional or national differences related with long-term results of childhood nephrotic syndrome.

Keywords: Child, nephrotic syndrome, course, treatment

Introduction
Nephrotic syndrome (NS) is a clinical picture characterized with severe proteinuria, hypoalbuminemia, edema and frequent hypercholesterolemia and hyperlipidemia and is one of the common chronic diseases observed in the childhood. Primary idiopathic NS constitutes 90% of NSs in the childhood and its incidence is 2-7/100 000 and prevalence is 16/100 000 in the childhood (1). Histopathologically, minimal lesion disease (MLD) is found with the highest rate. In addition, focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), mesangial proliferation, proliferative glomerulonephritis and membranous glomerulopathy may also be observed (2). The objective in treatment of nephrotic syndrome is to reduce proteinuria to the minimum level possible. The initial treatment is performed with corticosteroid. In patients who develop side effects related with corticosteroid or who do not respond to steroid, immunomodulator or immunosuppressive therapies are used. Preferences during use of these drugs which have effects on the immune system may show variance according to time and region. In the beginning, 80% of the patients generally respond to steroid and this shows good prognosis for the renal health (1). Thirty six-50% of the children who do not respond to steroid progress to end stage renal failure (ESRF) in 10 years (3, 4). These children who receive steroids repeatedly and for long-term carry a risk in terms of side effects including short stature, cataract.
and decreased bone mineral density. In addition, they may also develop side effects including neoplasia, hypertension and renal failure because of cytotoxic therapies including cyclophosphamide and cyclosporine (5). Current treatment approaches have shown hopeful outcomes in terms of treatment of the disease. However, their long-term side effects and ability to maintain remission are still being questioned. The aim of this study was to examine treatment responses, clinical course and complications of the patients who were diagnosed with primary nephrotic syndrome in a single center and to compare these with the other national and international data.

Material and Methods

The medical data of 33 patients aged between 6 months and 10 years who were diagnosed with idiopathic nephrotic syndrome between January 2000 and December 2012 in our center which gives tertiary health care service and followed up for a period of at least 2 years were reviewed. The patients who had insufficient data, who had an onset age below 6 months, who had hereditary or syndromic NS, who had a secondary cause and who had a follow-up period shorter than 2 years were not included in the study. Thirty tree of a total of 42 patients met these criteria. The following data were analyzed in our study:

1. History and clinical examination during the first evaluation
2. Demographic and anthropometric data
3. Laboratory variables at the first and final evaluations (urea, creatinine, albumin, total cholesterol, complete urinalysis, urine albumin/creatinine ratio or 24-hour urine protein)
4. Renal histopathology
5. Season of diagnosis
6. Immunosuppressive treatment
7. Complication type
8. Long-term outcome

A diagnosis of NS was made clinically in the patients who had edema, proteinuria (≥40 mg/m²/h), hypoalbuminemia (≤2.5 g/dL) and hyperlipidemia (6). Absence of albuminuria with urine dipstick test on three consecutive days (trace or negative) was considered remission and presence of ≥2+ albuminuria with urine dipstick test on three consecutive days was considered relapse. Remission which developed in the first 8 weeks after corticosteroid treatment was started was defined as steroid response. Long-term remission was defined as absence of relapse for three consecutive years. The patients who had a proteinuria level of 4-40 mg/m²/h in the absence of edema and a serum albumin level of >2.5 g/dL were considered to be in partial remission. Relapse more than two times in 6 months or more than four times in one year was defined as frequently recurring NS (7). At least two relapses while receiving prednisolone every other day or in 2 weeks after prednisolone was discontinued was defined as steroid-dependent NS (6).

The initial treatment of NS was administered as 60 mg/m²/day oral prednisolone (maximum 60 mg/day) for 4 weeks and subsequently 40 mg/m²/every other day for 4 weeks. The relapses were treated with 60 mg/m²/day (maximum 60 mg/day) prednisolone until remission was achieved and with 40 mg/m²/every other day prednisolone for 4 weeks after remission was achieved. The patients who did not respond to prednisolone treatment in the first 8 weeks were defined as steroid-resistant NS. In the patients who had frequently recurring NS or steroid-dependent NS, 60 mg/m²/day prednisolone (maximum 60 mg/day) was administered until remission was achieved and the lowest every other day dose maintaining remission without significant side effect was administered after remission was achieved. In the patients who had steroid-dependent or frequently recurring NS and who developed side effects of corticosteroid, cyclophosphamide at a dose of 2 mg/kg/day was administered for 12 weeks such that the cumulative dose was <180 mg/kg. Cyclosporine was initiated at a dose of 4-5 mg/kg/day in the patients who could not achieve complete or partial remission after this treatment and who had steroid-resistant NS such that the target blood level was 80-120 ng/mL.

Renal biopsy was performed in the patients who had an age of onset outside 1-10 years, who had accompanying macroscopic hematuria or hypertension, who were steroid-resistant and whose glomerular filtration rate was reduced despite cyclosporine treatment for longer than one year.

Short stature was defined as a height measurement below -2 standard deviation score. Hypertension was defined as a systolic or diastolic blood pressure measurement above the 95th percentile according age, height and gender (8). Bone mineral density (BMD) was tested once a year and ophtalmological examination was performed two times a year in the patients who received steroid treatment for longer than 3 months. A Z score
of <-2.0 according to age and gender in the bone mineral density test was defined as decreased BMD and the patients with a history of fracture in addition were defined to have osteoporosis (9).

**Statistical analysis**

Statistical analyses were performed using Windows 15.0 SPSS. The data were expressed as mean, percentage and range.

**Results**

Thirteen (39.4%) of 33 patients with idiopathic NS who were followed up for at least two years after the diagnosis were female and 20 (60.6%) were male. The mean age of disease onset was 3.2±2.04 years (range: 0.5-10 years) and the mean follow-up period was 6±3.4 years (range: 2-12 years). The age of disease onset was between 6 months and 1 year in two patients (6%) (NS of infancy). The disease onset season was spring in 7 (21%) patients, summer in 10 patients (30%), fall in 9 patients (27%) and winter in 7 patients (21%). No patient had a history of allergy. First-degree or second-degree consanguineous marriage was present in 5 patients (15.2%) and familial history of NS was present in one patient (3%) (Table 1).

In the beginning, 8 patients (24%) had hypertension and 6 patients (18%) had microscopic hematuria. None of the patients had renal failure. The mean serum albumin in the beginning was 1.98 g/dL (range: 0.8-2.1 g/dL).

According to responses to steroid treatment, 27 patient (81.8%) were defined as steroid responsive and 6 patients (18.1%) were steroid-resistant. In the steroid-responsive group, treatment response developed in the first 2 weeks in 13 patients (39%), in the 2-4th weeks in 10 patients (30%) and in the 4-6th weeks in 2 patients (6%). 6 (46.2%) of the patients who gave response in the first 2 weeks and 5 (50%) of the patients who gave response in the 2-4th weeks were in remission for a long time.

The histopathological diagnoses of 6 steroid-resistant patients who underwent biopsy included FSGS (n=3), C1q nephropathy (n=1), diffuse mesangial proliferation (n=1) and membraneous nephropathy (n=1). MLD (n=1) and diffuse mesangial proliferation (n=1) were found in two patients whose age of onset was <1 year. Diffuse mesangial proliferation was present in one patient who had macroscopic hematuria in the beginning.

FSGS was found in 2 patients who underwent biopsy because of increased serum creatinine level after cyclosporine treatment. The results of the patients who were followed up at least for two years were as follows: frequently recurring NS in five patients (15.2%), steroid-dependent NS in four patients (12.1%), steroid-resistant NS in 6 patients (18.2%) and other steroid-sensitive NS in 18 patients (54.5%) (Table 2).

Among 26 patients who were followed up for at least three years, 15 (57.7%) were followed up in prolonged remission, 5 (19.2%) were followed up with steroid-dependent NS, 4 (15.4%) were followed up with steroid-resistant NS and 2 (7.7%) were followed up with chronic renal failure.

<table>
<thead>
<tr>
<th>Table 1. Demographic and clinical properties of the subjects at baseline (n=33)</th>
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<tbody>
<tr>
<td>n %</td>
</tr>
<tr>
<td>Male/female 20/13 60.6/39.4</td>
</tr>
<tr>
<td>Ages of onset (mean 3.2 years) 0.5-10 years</td>
</tr>
<tr>
<td>Consanguineous marriage 5 15.2</td>
</tr>
<tr>
<td>Familial history of NS 1 3</td>
</tr>
<tr>
<td>Hypertension 8 24</td>
</tr>
<tr>
<td>Microscopic hematuria 6 18</td>
</tr>
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</table>

NS: nephrotic syndrome

<table>
<thead>
<tr>
<th>Table 2. Follow-up outcomes after the diagnosis of nephrotic syndrome</th>
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<tbody>
<tr>
<td>Minimum follow-up period</td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>% n</td>
</tr>
<tr>
<td>Remission</td>
</tr>
<tr>
<td>Steroid dependent</td>
</tr>
<tr>
<td>Steroid-resistant</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
</tbody>
</table>

*Patients with rare relapses were also included
*Five patients with frequently recurring NS were also included
sistant NS and 2 (7.7%) were followed up with chronic renal failure (CRF).

Among 11 patients who were followed up for at least five years, 3 (27.3%) were followed up in prolonged remission, 3 (27.3%) were followed up with steroid-dependent NS, 4 (36.4%) were followed up with steroid-resistant NS and 1 (9%) is still being followed up with CRF (Table 2).

In the frequently recurring group, the mean time of the first relapse was two months after steroid was discontinued (range 1-5 months). In these patients, a total of 76 relapses were observed and upper respiratory infection was found before relapse in 28 (36.8%) of these patients.

Cyclophosphamide was administered to 11 (33.3%) patients and cyclosporine was administered to 6 patients (18.2%). Full remission was achieved for a mean period of 19.4 months (range: 6-48 months) in 6 (54.5%) of the patients in whom cyclophosphamide was initiated. The results of 3 of 6 patients who had renal histopathology and who achieved full remission with cyclophosphamide were as follows: FSGS, MLD and diffuse mesangial proliferation. Full remission was achieved in 2 of the patients who used cyclosporine (histopathology: FSGS in one and diffuse mesangial proliferation in the other) during the time when they used the drug and partial remission was achieved in three patients (histopathology: FSGS in two and diffuse mesangial proliferation in one patient). Proteinuria recurred 2-8 months after treatment was discontinued in the patients who achieved full remission with cyclosporine. Angiotensin-converting enzyme-ACE was started simultaneously with their treatment in three patients who used cyclophosphamide and cyclosporine and were in partial remission. Both cyclophosphamide and cyclosporine were used in five (15%) patients throughout the follow-up period. Two of these patients are being followed up with full remission, one is being followed up with partial remission and one is being followed up with CRF (Table 3).

Hypertensive encephalopathy (n=1), glaucoma (n=1), peritonitis were found in the patients during treatment. Increased serum creatinine level (n=2) and leukopenia (n=1) were found with cyclosporine and leukopenia (n=3) was found with cyclophosphamide. Decreased BMD developed in three patients, short stature developed in 2 patients and cataract developed in 2 patients as complication (Table 4). The patients with short stature were investigated in terms of other causes of short stature, but no pathologic finding was found. Two patients who developed CRF were male and their ages of onset were 2 years and 5 years. Consanguineous marriage and hypertension at presentation were present in the history in both patients. In the beginning, partial remission was achieved with prednisolone and FSGS was found on histopathological examination.

Discussion

Idiopathic NS is the most common form of NS in the childhood. >90% of children between the ages of 1 and 15 years are affected with idiopathic NS. Despite the significant advances in the treatment of idiopathic NS, >50% of children who are diagnosed with idiopathic NS will experience relapses. The risk of relapse is higher in patients who present with elevated serum creatinine at the beginning of the disease. The risk of relapse is also higher in patients who have severe proteinuria, hypoalbuminemia and hypercholesterolemia. Despite the use of immunosuppressive drugs, 15%-20% of children who are diagnosed with idiopathic NS will continue to experience relapses. The risk of relapse is higher in patients who have high serum creatinine and proteinuria. The risk of relapse is also higher in patients who have severe proteinuria and hypoalbuminemia. The risk of relapse is also higher in patients who have severe proteinuria and hypoalbuminemia. The risk of relapse is also higher in patients who have severe proteinuria and hypoalbuminemia.

Table 3. Exposure to immunosuppressive drugs and response

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of days during which the drug was used</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>No response</th>
<th>Remission with medication (%)</th>
<th>Number of side effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>72 (120-30)</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>72.7</td>
<td>3</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>395 (90-660)</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>83</td>
<td>3</td>
</tr>
</tbody>
</table>

aThe results are given as mean and minimum-maximum range.
bComplete or partial remission at the end of treatment with a single immunosuppressive drug.

Table 4. Complications of nephrotic syndrome or its treatment

<table>
<thead>
<tr>
<th>Complication</th>
<th>Reduction in bone mineral density</th>
<th>Short stature</th>
<th>Cataract</th>
<th>CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid-dependent/frequently recurring NS</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Steroid-resistant</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

CRF: chronic renal failure; BMD: bone mineral density; NS: nephrotic syndrome
10 years diagnosed with NS have been reported to have idiopathic NS (10). Generally, it is known that patients with MLD on histopathological examination respond to steroid treatment well and patients with FSGS respond less. However, the long-term outcomes of the disease and treatment are still controversial.

In our study, there was a male predominance (1.5/1) and the mean age of onset was found to be 3.2 years. In other studies performed in our country, it was also reported that the disease was observed in male patients with a higher rate (1.4/1-2, 1/1) (11-14). The data about mean age of onset may show regional variations. The mean age of onset was found to be 5.2 and 6 years in the studies performed in Trabzon and Samsun, respectively and 3 and 3.9 years in the studies performed in Ankara and Konya, respectively (11-14).

Upper respiratory tract infections have been frequently questioned in terms of triggering both NS and relapses. In our study group, upper respiratory tract infection was not a triggering factor in initiation of NS. However, it was the main reason of the relapses in the frequently recurring group. Development of relapse following upper respiratory tract infections has also been noted by some investigators (15, 16). It has been recommended to switch the prednisolone dose to daily treatment for a short period of 5-7 days during intercurrent upper respiratory tract infection in NS patients with frequently recurring NS who receive maintenance prednisolone every other day in order to decrease the risk of relapse. This is practiced in our center (16, 17).

In our study the most common histopathological diagnosis was FSGS. When we examined the data from Turkey in this area, we found that the most common histopathological diagnoses included FSGS and MPGN in children who underwent biopsy with similar indications (13, 14, 18). On the other hand, international data have reported most commonly MLD and FSGS (16-19). Conclusively, FSGS histopathology may be observed predominantly in patients who do not have the clinical properties of MLD or who have steroid-resistant NS.

Response to steroid treatment is the most important prognostic factor (7). In our study, remission developed in the first 4 weeks in 73.3% of the patients who were in remission for a long term. Response to the initial treatment in the patients who progressed to CRF was in the form of partial remission. The data in our study support the importance of response to steroid treatment.

Ten-20% of the pediatric patients with idiopathic NS have a clinical picture of steroid-resistant NS and approximately 70% of these have FSGS on histopathological examination (19). In our study, the rate of steroid-resistant NS (18.2%) and the frequency of FSGS on histopathological examination (50%) were similar to the literature. According to the adult data, the chance of the kidney to be healthy after 5 years is 80%, if partial remission is observed in a patient with FSGS on histopathological examination (20). FSGS was found on histopathological examination in our patients who entered in the course of CRF and these patients gave partial remission response to steroid initially. However, the course of CRF started earlier in our patients. Probably, the localization of the underlying pathology (podocyte, slit diaphragm, glomerular basal membrane) and individual variations in pharmacokinetic effects (absorption, metabolism, distribution, excretion) caused to this outcome.

Children with a diagnosis of nephrotic syndrome may need steroid for a long-term, intermittently and at a high dose. This increases the risk for the side effects including steroid-induced cataract, short stature and osteoporosis. The incidence of cataract induced by long term steroid use is 10-14% (21, 22). Cataract which did not require operation developed in 6% of our patients.

In the literature, short stature has been reported with different rates (17.6% and 69.7%) depending on the follow-up period (mean: 47.4+/-30.5 months and 10 years total) in patients with idiopathic NS (23, 24). In our study, short stature which did not improve despite discontinuation of steroid treatment was found in 6% of our patients. It has been reported that short stature may not develop below a steroid dose of 0.75 mg/kg/day (25). In addition, improvement of short stature after discontinuation of steroid treatment has also been reported (26). The approach of administering the minimal dose which would provide remission for a long time in patients with steroid-dependent NS or frequently recurring NS in our center may be thought to have caused to the low rate of short stature in the study. However, short stature could not be prevented in a few patients despite this approach and switching to alternative therapies. It has been reported that long-term steroid treatment changes secretion and pulsatility of growth hormone and reduces serum insulin-like growth factor-1 and insulin like growth factor binding protein-3 levels (27-29). In clinical studies performed in Europe and USA; growth hormone treatment in the
prepubertal and pubertal periods was found to be efficient and safe in improving height standard deviation scores (30, 31). In patients with steroid-dependent NS, growth hormone treatment has been found to increase the level of insulin like growth factor-1 (32). In the literature, it was reported that an adolescent patient with short stature who was diagnosed with steroid-dependent NS was treated successfully with recombinant human growth hormone during usage of cyclosporine (33). Accordingly, it may be an appropriate approach to switch to steroid alternatives in the prepubertal or early pubertal period and keep in mind an individual growth hormone treatment option in order to prevent short stature in children with NS who require use of long-term steroid.

We found decreased BMD in the absence of fracture in 9% of the patients. Glucocorticoids inhibit osteoblastogenesis and stimulate osteoblast apoptosis and this leads to a reduction in bone formation (34). In adult studies, it has been reported that corticosteroids lead to bone loss and increase fracture risk in a dose-dependent fashion (35). Some studies have reported that osteoporosis develops with a rate of 1/3 in children diagnosed with frequently recurring NS (36). However, the rate of usage of calcium is considerably low in these studies (20%). In a population-based study, an increase in the risk of fracture was shown in children who required more than four courses of corticosteroid treatment (37). However, usage of calcium treatment was not evaluated in this study, either. In animal studies, it has been observed that corticosteroids used during growth reduce bone remodeling (38). This suggests that the growing skeleton may be more sensitive to glucocorticoids. In pediatric patients, the approaches targeting to decrease this risk include calcium and vitamin D supplements in combination with steroid treatment, administration of steroid treatment every other day and use of alternative drugs (39). In our center, 300-600 mg elementary calcium and 200-400 IU cholecalciferol treatment is initiated routinely in each patient who receives corticosteroids. Alternative therapies are used in patients who develop side effects related with steroid treatment. We think that this approach protects our patients against the risk of development of fracture. In a recent study, it was reported that vitamin D deficiency (75%, serum 25 OH vitamin D <20 ng/mL) and a decrease in BMD (%38, KMY Z-skor <-2) could be observed in children with a diagnosis of glomerulonephritis who received calcium and vitamin D supplements in combination with steroid treatment (40). Accordingly, vitamin D and calcium supplements given at a dose of daily requirement may not be sufficient in these patients. Serum vitamin D levels may need to be measured regularly.

In patients with a diagnosis of steroid-dependent NS, remission following cyclophosphamide has been reported with a rate of 31-35% in a mean follow-up period of five and six months (41, 42). In our patient group, full remission was observed with a rate of 54.5%. However, the mean remission time was 19.4 months and long-term remission could not be achieved in any of our patients. It has been reported that remission can be achieved with a rate of 85% with use of cyclosporine (43). In our study, full and partial remission were observed with a similar rate (83.3%). However, malignancy, infertility and nephrotoxicity are the most important factors which limit the use of these two agents in the long term. Nevertheless, cyclophosphamide and cyclosporine appear to be treatment options which assist in discontinuation of steroid treatment with side effects which can be reversed by close follow-up.

Conclusively, nephrotic syndrome is a clinical picture which may have side effects including chronic disease and treatment side effects, though the long-term outcomes are satisfactory. Therefore, pediatricians should screen their patients in terms of long-term side effects of steroid treatment including cataract, decreased BMD and short stature. Early recognition of these side effects should prompt switching to alternative therapies. It was observed that our response rates to steroid treatment were similar and the most common histopathological diagnosis was FSGS in our patients who underwent biopsy performed because of steroid-resistance. Multi-center studies will be helpful in demonstrating regional or national variations in long-term outcomes of childhood NS.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

**Informed Consent:** Written informed consent was obtained from patients’ parents who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - D.Ö.H.; Design - D.Ö.H., F.G.; Supervision - F.G., S.K.; Funding - D.Ö.H.; Materials - D.Ö.H., S.K.; Data Collection and/or Processing - D.Ö.H.; Analysis and/or Interpretation - D.Ö.H., F.G.; Literature Review - D.Ö.H.; Writer - D.Ö.H.; Critical Review - F.G.
Conflict of Interest: No conflict of interest was declared by the authors.

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References

28. Mehls O, Tönshoff B, Kovàcs G, Mayer C, Schurek J, Oh J. Interaction between glucocorticoids and growth hormo-
ne. Acta Paediatr Suppl 1993; 388: 77-82. [CrossRef]
[CrossRef]
30. Tönshoff B, Haffner D, Mehls O, et al. Efficacy and safety of growth hormone treatment in short children with al-
lografts: three years experience. Members of the German Study Group for Growth Hormone Treatment in Child-
31. Hokken-Koelega AC, Stijnen T, de Ridder MA, et al. Growth hormone treatment in growth-retarded adoles-
cents after renal transplant. Lancet 1994; 343: 1313-7. [CrossRef]
32. Zhou X, Loke KY, Pillai CC, How HK, Yap HK, Lee KO. IGFs and IGF-binding proteins in short children with steroid-dependent nephrotic syndrome on chronic glu-
ocorticoids: changes with 1 year exogenous GH. Eur J Endocrinol 2001; 144: 237-43. [CrossRef]
34. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids: potential mechanisms of their deleterious effects on bone. J Clin Invest 1998; 102: 274-82. [CrossRef]
39. Bak M, Serdaroglu E, Guclu R. Prophylactic calcium and vi-
tamin D treatments in steroid-treated children with neph-