INTRODUCTION

The principal hormones secreted by the thyroid are thyroxine (T4) and triiodothyronine (T3). Both these hormones maintain the level of metabolism in the tissues that is optimal for their normal function [1]. They play an important role in normal tissue growth and maturation, also having multiple effects on the neuromuscular system and the brain. As a result both hyperthyroidism and hypothyroidism may cause various neurological signs and symptoms [2]. In Hypothyroidism, as the thyroid hormone is not produced in enough amounts by thyroid gland, can be the cause of neuropathies. This may be caused by severe, long-term and untreated hypothyroidism. Alterations in peripheral nerves are well documented in cases of clinical hypothyroidism. The neuromuscular disorders are prevalent in thyroid dysfunctioning to about 20-80% [3]. It has been found to be associated with the myopathy, mononeuropathy, and sensorimotor poly neuropathy the condition of having multiple sensory, and motor neuropathies [4]. In hypothyroidism, the muscle contraction and relaxation are slowed down while duration is prolonged. Patients develop the usual manifestations of peripheral neuropathy. Loss of reflexes, weakness of proximal muscle, paraesthesia, decrease sensations e.g., vibration, joint-position, and touch-pressure.

In patients with clinically overt and undiagnosed hypothyroidism, peripheral nerves dysfunction may be the main manifestation with which patients can present to the OPD. There was also found the correlation of severity of neuromuscular symptoms and signs with the degree and duration of hormonal imbalance in clinical hypothyroidism [3]. It mainly depends on the severity and duration of the disease than to the severity of the thyroid hormone deficiency [2,4].

Many studies were conducted in past to find the presence of the polyneuropathy in association with hypothyroidism. The efforts were done to discuss the connection between hypothyroidism and polyneuropathy. Median nerve entrapment at the wrist is one of the most frequent cause of peripheral nerve damage in hypothyroidism [4]. It can be compressive neuropathy due to mucinous deposits in the peripheral nerves [5]. There can be intrinsic polyneuropathy which occurs due to metabolic disorder of Schwann cells in patients of hypothyroidism or due to segmental demyelination.

The prevalence of neuromuscular abnormalities was found in fifty eight newly diagnosed patients with hypothyroidism [2]. Neurophysiological studies revealed moderate reduction in conduction velocity with increased distal latencies of nerve action potentials.
in all four patients studied[4]. Khedar et al examined twenty three patients with hypothyroidism and found 52% had peripheral nervous system involvement with entrapment neuropathy in 35% of patients [6]. In a case-control cross-sectional study, forty patients with untreated primary hypothyroidism were electrophysiologically examined and neurological abnormalities were observed [7]. The decreased conduction velocity and amplitudes were found by Lai et al in fourteen patients on peripheral nerve conduction studies [8]. It was also suggested that a considerable number of untreated hypothyroid patients may have preclinical asymptomatic small-fiber sensory neuropathy [9]. Yuksel et al investigated the electrophysiological changes in subclinical hypothyroid patients and observed that median motor and sensorial nerves were the most commonly affected nerves with carpal tunnel syndrome positive in 54.5 % and sensorimotor polyneuropathy in 8-9% of patients [10] Only a few studies have evaluated the functional alterations in central and peripheral nervous systems in subjects with subclinical hypothyroidism [11,12] and found no significant impairment in peripheral nerve function in subclinical hypothyroidism. Mostly, the hormone replacement therapy might reverse the biochemical abnormalities and restores the nerve function. In hypothyroid patients, the entrapment neuropathy and polyneuropathy can be reversed with the appropriate and timely hormone (thyroxine) replacement treatment especially in the case of entrapment neuropathy [13]. After treatment, peripheral conduction velocities found to return to normal limits with the abnormality in amplitude still persisted as studied by Lai et al [8].

As published data is available regarding the normal values of nerve conduction parameters of healthy punjabi population, but no published data has been found on nerve conduction parameters in hypothyroid patients. In Punjab, a good number of patients are suffering from hypothyroidism which varies in severity as well as duration of disease. Most of the patients are not aware about the consequences as well as the neurological complications to the General medicine/Orthopaedics outpatient department.

AIMS and OBJECTIVES
1. To investigate the presence of Electrodiagnostic abnormalities in the selected nerves in patients with newly diagnosed hypothyroidism and compare their mean± SD values with that of euthyroid controls.
2. To correlate the findings with existing neurological signs and symptoms.
3. To intervene at the earliest so that neurological damage can be reversed by treatment.

MATERIALS:
A Prospective study was performed at our institute over a duration of ten months. In the study, forty adult females of mean± SD age 30.42 ± 2.45 yrs (range 21-45yrs), the newly diagnosed cases of hypothyroidism were taken as subjects. Forty normal, healthy, females of mean± SD age 31.36 ± 1.46 yrs acting as controls who were not diagnosed for any thyroid disease. A patient information sheet was prepared and informed consent was taken.

Inclusion criteria
The female patients of age (range 21-45yrs), with the newly diagnosed hypothyroidism (before the start of treatment) presenting with neurological or other clinical manifestations to the General medicine/Orthopaedics outpatient department.

Exclusion criteria
The patients diagnosed with hyperthyroidism, female patients with pregnancy, all the pts with past or family History of other possible causes of neuropathy or neuromuscular diseases, H/O alcoholism, Past H/O diabetes mellitus, liver and kidney disease, use of drugs known to cause neuropathy or myopathy, malignancy or other serious illness.

METHODS
The patients were asked whether these symptoms were their first or main complaints, when they firstly visited to the OPD. They were evaluated first by detailed general physical and neurological examination. Then the biochemical profile was evaluated to confirm the diagnosis of hypothyroidism and detailed electro-diagnostic studies were conducted. Thyroid function tests including serum TSH, free T3 and free T4 measurements were carried out by radioimmunoassay methods. All these examinations were done at entry, when patients were still untreated. They were questioned regarding date of diagnosis of hypothyroidism. For the history about neurological dysfunctions, a questionnaire was used with attention given to motor as well as sensory symptoms. Then an initial appropriate dose of thyroid replacement therapy was started.

The detailed clinical and neurological examination was performed by the experienced examiner. The height and weight of all patients was measured in all visits and body mass index (BMI) of each patient was calculated. The neurological examination consisted of motor and sensory system separately on all the patients. For the motor system examination, the assessment of strength of major muscle groups on the both sides (flexors and extensors of neck, flexors and extensors of elbow and wrist, flexors and extensors of knee, dorsi-flexors and plantar
flexors of foot) was done. The tendon reflexes were also performed and graded according to standard Mayo’s scale. The sensory modalities (tactile sensibility ie. fine /gross touch, 2-point discrimination testing, pin prick, and vibration sense) were tested and graded according to a standard protocol. Also the examination for thenar muscle atrophy and weakness, the Phalen’s test and Tinel’s sign at the wrist were done on all the patients having hand signs and symptoms.

These electro-diagnostic studies were performed in the research lab in dept. of Physiology, at our institute after taking the informed consent from the patient. The electro-diagnostic procedure was be carried out with the help of Clarity vision NCS/EMG Machine, according to standardised protocols to obtain and record the action potentials for the motor and the sensory nerves[14]. The subjects were examined while sitting for the upper limb and lying comfortably on the couch in the supine position. The room temperature was kept at 25-28°C. The skin was adequately swabbed with methylated spirit before the application of the stimulating and recording electrodes, to ensure good contact between these electrodes and the skin.

The filters were set at 2 Hz to 5 kHz for the motor studies and at 20 Hz to 2 kHz for the sensory studies. The sweep speed wereset at 5ms/division for the motor studies and 2 ms/division for the sensory studies. A stimulus duration of 50 -1000 μs and a current of 0–100 mA will be required for an effective nerve stimulation after delivering supramaximal stimuli in order to get adequate responses. The surface fixed stimulating electrodes and the surface 1cm disc recording electrodes were used for the motor and the sensory studies. The ground electrode is place on the limb to be tested between the recording and stimulating electrodes.

The nerve conduction studies were performed on median and ulnar nerves B/L in upper limb and common peroneal nerve, tibial and sural in the lower limb B/L to compare the sensory as well as the motor parameters of these nerves with that of controls. The most commonly involved nerves are the sural nerve and median nerve sensory fibers, as the distal and sensory nerves are affected earlier [2].

The study included: 1) Motor nerve conduction studies - Determination of motor latency (DL),motor amplitudes (CMAPs) and motor conduction velocity (MNCV) in median and ulnar nerves in the upper limb while peroneal and tibial nerves in the both lower limbs after distal and proximal stimulation of the nerves. Also F- wave minimal latencies for the motor median, ulnar and tibial nerves were determined bilaterally.

The median and ulnar nerves were stimulated 8 cm above the active recording electrode at the wrist distally and at the elbow in the antecubital space proximally. The muscle potentials were recorded from abductor pollicis brevis and abductor digitii minimi respectively. The deep peroneal nerve was stimulated distally 8 cm above the active recording electrode at the ankle and proximally at head of fibula and below the tuberosity of the fibula and ankle conduction velocity was recorded. The tibial nerves were stimulated distally 8 cm above active recording electrode posterior to the medial malleolus and proximally in popliteal fossa. The muscle potentials were recorded from the abductor hallucis muscle. Sensory nerve conduction studies – Determination of sensory latency (SL), sensory amplitudes (SNAPs) and sensory conduction velocities (SNCV) of median and ulnar nerves in both upper limbs orthodromically. Also sural and superficial peroneal nerves in the both lower limbs anti-dromically.

Palm-wrist sensory conduction of median and ulnar nerves was determined (stimulus 8 cm distal to active electrode on the wrist, with the distance between active and recording electrode about 3-4cm). For the sural nerve sensory parameters, proximal segment conduction was done with an active recording electrode placed between the lateral malleolus and the Achilles tendon, with electrical stimulation applied 14 cm proximal to the active electrode right below the ventral part of gastrocnemius muscle. For the superficial peroneal sensory parameters, the active recording electrode was placed on the lateral 1/3 between both two malleoli, and stimulation was applied on the calf region approx 14cm proximal to the active electrode.

The motor distal, F-minimal and sensory latencies, amplitudes and conduction velocities between the median and ulnar nerves were compared to establish the diagnosis of median nerve compression at wrist (conventional conduction studies). The sensory and motor nerve conduction studies (NCS) of the median nerve segment across the wrist compared to another nerve such as ulnar nerve,are the most sensitive and accurate techniques for making a diagnosis of Carpal tunnel syndrome [15].

ETHICS:
The study was approved by our institutional research and ethics committee. The study was done without the usage of any chemical /drug and animals.

STATISTICAL ANALYSIS:
The statistical analysis was carried out. The data will be expressed as mean ± SD and the p values<0.05 will be taken as significant , (p-value < 0.001): highly significant and (p-value >0.05): NS =Non-significant.

RESULTS AND DISCUSSION
Hypothyroidism is a clinical condition associated with low levels of thyroid hormones with variably raised TSH. There can be present two different types of peripheral neurological abnormalities
associated with hypothyroidism. Carpal tunnel syndrome (CTS), a type of mononeuropathy occurring due to Median nerve entrapment at the wrist is one of the most frequent causes of peripheral nerve damage in hypothyroidism with the much variable incidence, but sensory-motor polyneuropathies can also be seen [4]. In hypothyroid patients, median motor and sensory nerves are the most commonly affected nerves. Hypothyroidism is commonly included as an important risk factor for carpal tunnel syndrome (CTS), yet this association between the two is not defined in any study (16). Some reports suggest that axonal demyelination can result in peripheral mononeuropathy, polyneuropathy or entrapment neuropathies in hypothyroidism [17].

In the present study, we evaluated the clinical, biochemical and electro-physiological findings in newly diagnosed hypothyroid patients. In the study period, forty patients with untreated hypothyroidism fulfilled the inclusion and exclusion criteria and participated in the study. Equal no. of age and sex matched subjects were taken as controls. All the patients were women (100%).

On History and Clinical examination

Thirty five (88%) patients presented with history of neurological complaints in one/both upper or lower limbs rather than the other general clinical manifestations of thyroid disease as their chief complaints. Out of these, twenty two (63%) had muscle weakness in one or more muscles. Of these, fourteen patients (64%) presented with upper limb weakness, marked muscle fatiguability, stiffness and cramps while eight patients (36%) complained of lower limb weakness. Out of total symptomatic patients, thirty (86%) patients had also presented with sensory complaints in the 3/4 fingers of one or both hands such as pain/burning pain especially aggravated at night, some had pain, sometimes radiating proximally into the fore- and upper arm, parasthesias (sensation of pins-and-needles), tingling and numbness. Further, out of thirty patients, seven (23%) also had associated sensory complaints such as pain, parasthesia, tingling and numbness in the lower limbs. Only five (14%) had the isolated sensory complaints in lower limbs. The mean subjective duration of these symptoms was 12.9±2.6 months. On examination, there was observed decreased muscle strengths in three or more muscle groups in twenty patients. The sensations in both hands and feet were tested with touch, pinprick and/or two-point discrimination and found to be decreased or absent in area of distribution of median nerve in one or both hands in twenty-eighty patients (93%) and in feet and lower lateral aspect of legs in twelve patients (40%), out of total thirty symptomatic patients. Then patients were tested for thenar muscle atrophy and weakness, also the Phalen’s test and Tinel’s sign at the wrist. These test results were found to be positive in only twenty five patients (71%).

In table 1 and Fig.a) The mean ±SD values of serum concentrations of TSH, FT3 and FT4 in patient and control groups along with anthropometric measurements eg., Age, height, weight and BMI have been documented in table 1. The age and height (mean ±SD) was 30.4 yrs±2.45 yrs and 153.78±3.23 in comparison to 31.3 yrs±1.46yrs and 155.34±2.45 in controls, showing non-significant association (p>0.05). Both FT3 and FT4 levels were significantly (p<0.01) lower in hypothyroids in comparison to those of controls. Also TSH concentrations were significantly higher in patients than in controls (p<0.01). As shown in Fig 1), in patients, BMI at 1st visit was observed to be 26.91±2.13 significantly higher than the control group (23.41±1.89).

Table 2 and 3. show the electro-diagnostic findings in both the upper and lower limbs in hypothyroids vs controls respectively. Mean± SD values were compared with that of equal no. of controls. Most of our findings are compatible with the literature studied.

According to table 2 and Fig. 2a) and 2b), In the upper limb in median nerve in hypothyroidism patients as compared to controls, Distal latency (DL) was 4.24±1.23 msec vs 3.10±0.60 msec and F-minimal latency was 27.09 ± 2.45 ms vs 24.05± 2.32 ms respectively. The motor amplitudes (CMAP) were also decreased in the median nerve. 7.68±1.41 mv vs 12.60±3.10 mv in controls. The motor nerve conduction velocity (MNCV) in the median nerve is highly decreased to 42.99±3.45m/sec. The sensory latency (SL) in hypothyroid patients compared to controls was found to be 2.86±0.45 ms vs 1.45±0.25 ms and amplitude (SNAP) 23.04±10.11mv vs 33.14±8.43 mv respectively. The SNCV was 44.89±8.63/msec vs 51.17±7.82 m/sec in controls. Thus, the measurements in median nerve showed highly significant differences between hypothyroidism pts and controls. When compared with the control group, as shown, DL of the median nerve was highly significantly (p<0.01) prolonged in patients of hypothyroidism along with the significant prolongation of F-wave minimal latency; the motor amplitude and MNCV in hypothyroid patients were highly significantly decreased, results agreed with the results of other researchers (2,3,18). In sensory parameters, SL of the median nerve was highly significantly prolonged, finding consistent with other studies (2,6,13,18), and the amplitude and sensory conduction velocity(SNCV) of the median nerve in hypothyroid patients was highly significantly decreased ,finding almost similar with other studies (2,6,13,18).

As shown in table 2 and Fig 3a) and 3b), The Ulnar nerve parameters (distal motor, F-minimal wave latencies and sensory latencies, motor and sensory amplitudes and nerve conduction velocities) were found to be normal in hypothyroid patients as compared with

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controls. There was statistically non-significant association (p>0.05). In ulnar nerve conduction parameters in hypothyroid patients, the results agreed with other study [2] but varying from study of Nemni et al [4].

According to table 3 and Fig.4a) and 4b), the motor parameters in the lower limbs are shown. There occurs shortening of the amplitudes (CMAPs) in both the deep peroneal and tibial motor nerves is observed when compared to controls and found to be statistically significant. There is also seen significant prolongation of DL of both nerves and F-wave latency of tibial nerves. The motor nerve conduction velocities are also significantly decreased in both the nerves. The results of peroneal nerve conduction agreed with [4,18]. However findings of tibial nerve conduction being significantly affected, didn’t agree with the results of other studies [2, 6].

Also shown in table 3 and Fig.5a), the sensory parameters in lower limbs for sural nerve (proximal segment) in hypothyroid patients highly significant differences were observed in sensory nerve conduction velocity (SNCV) as compared to controls, results agreed with the results of other studies [2,13]. The sensory latency (SL) is highly significantly prolonged and amplitude is highly significantly decreased. These results agreed with many researchers[2,4,6,13]. According to Fig. 5b) in case of superficial peroneal nerve in hypothyroid patients as compared to controls, the sensory latency is significantly prolonged and amplitudes highly significantly while sensory nerve conduction velocity (SNCV) was significantly decreased. No referred data was available to compare these nerve conduction parameters. Superficial peroneal nerve was also included in the study because according to some researchers, the superficial peroneal sensory nerve and its distal branches are more useful as diagnostic criteria of peripheral neuropathy than the sural nerve alone[19]. So, these studies can be used as a standard diagnostic tool for screening and diagnosing early polynuropathy / peripheral neuropathy of the lower limbs.

All the controls had normal clinical and neurological examination and normal electro-diagnostic studies results. In the patients with hypothyroidism, the compression neuropathy of the median nerve at the wrist (mononeuropathy / carpal tunnel syndrome, CTS) was established on the basis of abnormal values of distal motor and/or sensory latencies and comparative values of sensory latency (SL) and SNCV between median and ulnar nerves in palm-wrist conduction as per established standards. The abnormal median nerve electro-diagnostic findings suggestive of Carpal tunnel syndrome (CTS) due to median nerve compression at wrist was observed in twenty seven patients (67.5%), out of which twenty six (97%) were symptomatic. Out of these patients with CTS, twenty two (81%) patients had isolated CTS (without any other neuropathy). In five patients (19%), CTS is present associated with abnormal electrodiagnostic tests in lower limb nerves suggestive of sensorimotor polyneuropathy. Out of total patients, five patients 12.5%) had isolated sural neuropathy and four patients (10%) patients had also isolated sensorimmotor polyneuropathy and total ten patients with sensorimotor polyneuropathy (25%) as detected by the electrodiagnostic tests.

Table 1: Biochemical and anthropometric parameters in hypothyroid subjects vs controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypothyroid subjects (N=40)</th>
<th>Euthyroid (controls) (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean FT3 (ng/ml)</td>
<td>0.48 ±0.04 *</td>
<td>2.52 ±0.15</td>
</tr>
<tr>
<td>Mean FT4 (ng/dl)</td>
<td>0.59 ±0.75*</td>
<td>1.24 ±0.02</td>
</tr>
<tr>
<td>Mean TSH (µIU/mL)</td>
<td>9.17±2.19*</td>
<td>2.39±1.07</td>
</tr>
<tr>
<td>Age (y) (mean ±SD)</td>
<td>30.42±2.45</td>
<td>31.36 ± 1.46</td>
</tr>
<tr>
<td>(Height (cm) (mean ±SD)</td>
<td>153.78±3.23*</td>
<td>155.34±2.45</td>
</tr>
<tr>
<td>Weight (Kgs)</td>
<td>63.64 ± 4.21*</td>
<td>56.51± 3.73</td>
</tr>
<tr>
<td>BMI at 1st visit</td>
<td>26.91±2.13*</td>
<td>23.41±1.89</td>
</tr>
</tbody>
</table>

* = significant (p-value < 0.05); ** = highly significant (p-value < 0.001), NS = Non-significant(p-value >0.05)
Table 2: Electrodiagnostic findings in the upper limbs in hypothyroid subjects vs controls (Mean ±SD).

<table>
<thead>
<tr>
<th>UPPER LIMB</th>
<th>Hypothyroid subjects (Mean±SD)</th>
<th>Controls (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Motor</td>
<td>Sensory</td>
</tr>
<tr>
<td></td>
<td>DL(ms)</td>
<td>MNCV (m/sec)</td>
</tr>
<tr>
<td>Median</td>
<td>4.24±1.23**</td>
<td>42.99±3.45**</td>
</tr>
<tr>
<td>Ulnar</td>
<td>2.19±0.41</td>
<td>60.55±4.13</td>
</tr>
</tbody>
</table>

2) Sensory

<table>
<thead>
<tr>
<th>LOWER LIMB</th>
<th>Hypothyroid subjects (Mean±SD)</th>
<th>Controls (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Motor</td>
<td>Sensory</td>
</tr>
<tr>
<td></td>
<td>DL(ms)</td>
<td>NCV(m/sec)</td>
</tr>
<tr>
<td>Median</td>
<td>4.67±1.24*</td>
<td>44.19±2.21*</td>
</tr>
<tr>
<td>Tibial N.</td>
<td>4.13±0.27*</td>
<td>42.29±1.28*</td>
</tr>
</tbody>
</table>

2) Sensory

| SUPERFICIAL PERONEAL N. | 1.95±0.15 | 43.08±2.56 | 4.70±1.21** | 1.45±1.01 | 46.76±3.28 | 9.71±0.86 |
| SUPERFICIAL SURAL N.    | 2.15±0.56 | 40.81±3.52 | 10.17±2.01*** | 1.55±0.23 | 46.45±1.78 | 18.10±1.89 |

* = significant (p-value < 0.05); ** = highly significant (p-value < 0.001), NS = Non-significant (p-value >0.05)

Table 3: Electrodiagnostic findings in the lower limbs in hypothyroid subjects vs controls (Mean ±SD).

Table 4: % age of Electro-diagnostic abnormalities in both the limbs in hypothyroid subjects.
Fig-1a: Showing mean ±SD values of serum concentrations of TSH, FT3 and FT4 and anthropometric measurements in hypothyroid patients and controls.

Fig-2a: Showing Median motor nerve conduction values (mean ± SD).

Fig-3a: Showing Ulnar motor nerve conduction values (mean ± SD)
Fig. 2b: Showing Median sensory nerve conduction values (mean ± SD)

Fig. 3b: Showing Ulnar sensory nerve conduction values (mean ± SD)

Fig. 4a: Showing Deep peroneal motor nerve conduction values (mean ± SD)
CONCLUSION

It is concluded that in hypothyroidism, there occurs the impairment of peripheral nerves motor as well as sensory nerve functions, sensory functions being affected more than motor functions. This study has been done to find out nerve conduction status of some selected peripheral nerves in both limbs to evaluate existence of the mono/ polyneuropathies in hypothyroid patients at an early stage even in asymptomatic. So, that the timely hormone treatment can be initiated soon in order to ameliorate neurological complaints and prevent future complications.
ACKNOWLEDGEMENT:

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REFERENCES