

# Growth hormone therapy at the time of Covid-19 pandemic: adherence and drug supply issues

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From the end of February 2020 the organisation of many hospitals in Italy, as well as all over the world, has changed dramatically, to face the increasing emergency of COVID 2019 pandemic.

As endocrinologists, we continue to deliver urgent care to our patients when needed, trying to grant assistance to our chronic and frail subjects as well. The Endocrinology Unit at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan is a Reference Centre for diagnosis and treatment of growth hormone (GH) deficiency (GHD) in the paediatric, transition and adult population. Our experience in this field is long lasting and particularly focused on the impact of GH therapy on other hypothalamic–pituitary axis (1, 2).

Facing the emergency of COVID-19 in one of the first red zones in Italy, we report our experience and strategies in the management of patients with GHD in whom, as in many chronic diseases, adherence to treatment is one of the main concern and significantly affects outcomes.

In this peculiar situation, we decided to call our GHD patients/families to ask them about their clinical conditions, to discuss laboratory results when available and to reinforce the importance of staying at home as indicated. Meanwhile, we inquired also on possible modification of their adherence to therapies during pandemic time, including GH replacement.

## Methods

Between 13 and 30 April 2020, we contacted our entire cohort of GHD patients on active follow-up, including

208 subjects. None of them reported a confirmed SARS-CoV2 infection, with only three adults complaining suggestive symptoms in the past 2 months. When asking for adherence, verbal informed consent was obtained from patients or parents before starting the interview.

In the paediatric population, adherence was assessed using the eight-item Morisky Medication Adherence Scale (MMAS), as reported in a recent paediatric cross-sectional study (3). The scale is composed of eight items, scored as 0 or 1 according to the answer to each different item. A patient is considered highly adherent if the total is 8, while scores between 6.0 and 7.9 and less than 6 are categorized as medium and low adherence, respectively (4). For each item, when applicable, we asked parents to refer answers from the last month.

For adults and transition population, adherence to GH therapy was measured by the auto-compliance method that estimates the number of missed GH injections during the previous month, according to the methodology designed by Haynes *et al.* (5). Patient self-reported difficulty in taking the medication is recorded by asking two open questions: (1) 'Did you have any difficulties in GH injection?' and (2) 'How many times did you skip GH injection in the last month?'. Adherence was calculated by dividing the number of GH injections with the total number of prescribed GH injections during the last month and reported as a percentage. Patients who declared taking more than 80% of the total number of the prescribed GH injections were considered adherent.

## Paediatric population

The paediatric population was composed of 107 patients (60M, mean age:  $11.3 \pm 3.5$  years). Analysing adherence, the group was further divided into children ( $n=58$ , mean age:  $8.8 \pm 2.5$ , range: 1.2–12 years) and adolescents ( $n=49$ , mean age:  $14.4 \pm 1.5$ , range: 12.2–17.8). According to MMAS scale, 82.2% of patients were highly adherent ( $n=88$ ), while 13.1% ( $n=14$ ) and 4.7% ( $n=5$ ) showed intermediate and low adherence, respectively. Evaluating separately children and adolescents, more than 80% of patients were highly adherent in each group (MMAS score=8), while a difference emerged in the prevalence of low adherence (MMAS score <6), being almost five-fold higher in the older group: 8.2% ( $n=4$ ) and 1.7% ( $n=1$ ) in adolescents and children, respectively. Notably, three out of five patients missed injections in the last period due to problems related to drug supply that we managed to solve, while one is a 17-year-old adolescent with GHD in hypopituitarism, who showed a serious need to be convinced on the importance of his compliance to hormone replacement therapies. The present results are strikingly higher than those reported in the previous study using MMAS: 16.6% of high adherence, 40.8% and 42.6% of intermediate and low adherence, respectively (3). Conversely, in a multicenter Italian study, 72.1% of participants reported that they never missed an injection during a typical week (6).

## Adult and transition population

The adult group was composed of 101 patients: (92 adults, 42 males, mean age:  $54 \pm 12$  years, and 9 patients in the transition age, 6 males, mean age:  $19 \pm 2$  years). This cohort was mostly composed of patients with organic hypothalamic–pituitary diseases, multiple hormone deficiencies and complex replacement therapies, thus we use the previously described method as it is very simple and rapid to answer to. The questions specifically refer to the previous month, reflecting the peak of Covid-19 pandemic in our country, and are the same that we usually address to patients during each visit. According to this method, 94% of the patients declared to have an acceptable GH-adherence. (Non-adherence) Missed injections were in most cases (four out of six) due to drug supply, which we managed to solve together. Previous relevant studies on GH adherence in adults have recently been reviewed (7) and showed a globally good adherence

rate (70–91.3% of patients missing less than one injection per week). As it is known that adherence might be lower in the transition period, we analysed the two groups separately and obtained similar results.

## Conclusions

Most of our GHD patients showed good adherence to GH therapy, even in this period of sanitary emergency wherein health concerns are globally focused on Covid-19. As for patients with a recent start of GH therapy, fortunately they did not complain of any adverse effects and also showed good adherence. In the non-pandemic era, adherence to GH therapy has been repeatedly demonstrated to be suboptimal, regardless of the assessment method used, being generally best in adulthood and worst in adolescence, with intermediate rates in childhood (7, 8). This report refers to an extraordinary time, thus comparison with previous literature data is difficult, also because of the heterogeneity of methods used. Namely, the auto-compliance due to its self-reported nature may overestimate adherence (4), but it proved to be the easiest one in this exceptional situation. Present rates are similar or even higher than those previously reported, especially in paediatric patients, and that is a remarkable point. Overnight trips or being away from home have been reported as frequent reasons for skipping injections both in children and adults (3, 9). Hence, the unusual situation of being confined at home due to the Covid pandemic might be hypothesized as a possible aspect influencing the high adherence rate recorded here. However, drug shortage and inaccessibility to the pharmacy were listed as barriers too (3).

Poor adherence to GH therapy, especially if prolonged, is particularly detrimental for growth in children and adolescents. In adults, even though short-term discontinuation does not affect long-term outcomes (10), it is well known that poor compliance may affect general health (7). For this reason, we enquired about adherence at each visit. Revising patients' records of the previous year, we found adherence rates similar to those reported here (unpublished data).

For GHD, as for many endocrine conditions, self-management is of crucial importance (11). Providing a picture of GH adherence during Covid-19 pandemic from one of the first and worst hit European country, we aim to share our experience in the management of both paediatric and adult patients. By means of telephone calls,

we supported patients' and families' awareness on the importance of their chronic therapy and could help them solve problems related to drug supply.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this letter.

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