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Article

Oral Iron Absorption of Ferric Citrate Hydrate and Hepcidin-25 in Hemodialysis Patients: A Prospective, Multicenter, Observational Riona-Oral Iron Absorption Trial

Naohisa Tomosugi [1,*], Yoshitaka Koshino [2], Chie Ogawa [3], Kunimi Maeda [4], Noriaki Shimada [5], Kimio Tomita [6], Shoichiro Daimon [7], Tsutomu Shikano [8], Kazuyuki Ryu [8], Toru Takatani [9], Kazuya Sakamoto [10], Satonori Ueyama [11], Daisuke Nagasaku [12], Masato Nakamura [13], Shibun Ra [14], Masataka Nishimura [15], Chieko Takagi [16], Yoji Ishii [17], Noritoshi Kudo [18], Shinsuke Takechi [19], Takashi Ishizu [20], Takamoto Yanagawa [20], Masamichi Fukuda [21], Yutaka Nitta [22], Takayuki Yamaoka [22], Taku Saito [23], Suzuko Imayoshi [23], Momoyo Omata [24], Joji Oshima [25], Akira Onozaki [26], Hiroaki Ichihashi [27], Yasuhisa Matsushima [28], Hisahito Takae [29], Ryoichi Nakazawa [30], Koichi Ikeda [31], Masato Tsuboi [32], Keiko Konishi [33], Shouzaburo Kato [34], Maki Ooura [35], Masaki Koyama [36], Tsukasa Naganuma [37], Makoto Ogi [38], Shigeyuki Katayama [39], Toshiaki Okumura [40], Shigemi Kameda [41] and Sayuri Shirai [42]

1 Division of Systems Bioscience for Drug Discovery, Project Research Center, Medical Research Institute, Kanazawa Medical University, Kahoku 920-0293, Ishikawa, Japan
2 Mizuho Hospital, Tsubata 929-0346, Ishikawa, Japan; mizuho@tiara.ocn.ne.jp
3 Maeda Institute of Renal Research Musashikosugi, Kawasaki 211-0063, Kanagawa, Japan; tato.ogawa@gmail.com
4 Maeda Institute of Renal Research Shakujii, Nerima 177-0041, Tokyo, Japan; kuni@maeda-irr.com
5 Tachibana Clinic, Sumida 131-0043, Tokyo, Japan; noriaki.shimada@tachibana-cl.or.jp
6 The Chronic Kidney Disease Research Center, Tomei Atsugi General Hospital, Atsugi 243-8571, Kanagawa, Japan; tomyw23@nifty.com
7 Department of Nephrology, Daimon Clinic for Internal Medicine, Nonoichi 921-8802, Ishikawa, Japan; dai-clinic@m2.spacelan.ne.jp
8 Kyoto Okamoto Memorial Hospital, Kuze 613-0034, Kyoto, Japan; sktu@okamoto-hp.or.jp (T.S.); ryu.kazuyuki@gmail.com (K.R.)
9 Nephrology Division, Tojinkai Hospital, Fushimi 612-8026, Kyoto, Japan; takatani@tojinkai.jp
10 Department of Urology, Tomakomai Nisshou Hospital, Tomakomai 053-0803, Hokkaido, Japan; k.sakamoto@nisshou-hospital.jp
11 Jinaikai Ueyama Hospital, Kagoshima 890-0073, Kagoshima, Japan; s-ueyama@jin-ai-kai.or.jp
12 Yujin-Yamazaki Hospital, Hikone 522-0044, Shiga, Japan; nagasaku@simosaka.jp
13 Susono Daiichi Clinic, Susono 410-1112, Shizuoka, Japan; susonoce@joy.ocn.ne.jp
14 Noheji Clinic, Noheji 039-3152, Aomori, Japan; kashiranodagashira@yahoo.co.jp
15 Shimosaka Clinic, Nagahama 526-0044, Shiga, Japan; nishimura@simosaka.jp
16 Ohgo Clinic, Maebashi 371-0232, Gunma, Japan; chiekot@cj8.so-net.ne.jp
17 Nozatomon Clinic, Himeji 670-0011, Hyogo, Japan; touseki@nozatomon.jp
18 Kowa Clinic, Goshogawara 037-0066, Aomori, Japan; kowa@hakuseikai.com
19 Takechi Clinic, Iyo 791-3141, Ehime, Japan; ikei@takechi-clinic.jp
20 Department of Nephrology, Tsukuba Central Hospital, Ushiku 300-1211, Ibaraki, Japan; takasi.isizu@gmail.com (T.I.); yana_3173@yahoo.co.jp (T.Y.)
21 Iwakuni Medical Center, Iwakuni 740-0021, Yamaguchi, Japan; mami9380@yahoo.co.jp
22 The Department of Nephrology, Saiseikai Shimonoseki General Hospital, Shimonoseki 759-6603, Yamaguchi, Japan; y-nitta@simo.saiseikai.or.jp (Y.N.); simosai.jinnai.2018@gmail.com (T.Y.)
23 Saito Memorial Hospital, Kawaguchi 332-0034, Saitama, Japan; saitoukinen@med.email.ne.jp (T.S.); papamia888@yahoo.co.jp (S.I.)
24 Department of Internal Medicine, Hachioji Azumacho Clinic, Hachioji-shi 192-0082, Tokyo, Japan; m-omata@juno.ocn.ne.jp
25 Kubojima Clinic, Kumagaya 360-0831, Saitama, Japan; jo123kum@sakitama.or.jp
26 Tokatsu-Clinic Hospital, Matsudo 271-0067, Chiba, Japan; anzen.tch@mbr.nifty.com
27 Tokatsu Clinic Yabashira, Matsudo 270-2253, Chiba, Japan; tc-yahashira@nifty.com
28 Tokatsu Clinic Kashiwa, Kashiwa 277-0005, Chiba, Japan; tc-kasiwa@nifty.com
29 Tokatsu Clinic Matsudo, Matsudo 271-0077, Chiba, Japan; tc-matudo@nifty.com
30 Tokatsu Clinic Mirai, Matsudo 271-0091, Chiba, Japan; r.nakazawa@mbr.nifty.com
31 Tokatsu Clinic Koiwa, Edogawa 133-0056, Tokyo, Japan; tomosuginaohisa@gmail.com
32 Kaikoukai Anjo Kyoritsu Clinic, Anjo 446-0065, Aichi, Japan; m-tsuboi@kaikou.or.jp

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[33] Seiwa Hospital, Toyama 931-8431, Toyama, Japan; seiwakeiko7002@yahoo.co.jp
[34] Nishi Interchange Clinic for Internal Medicine and Dialysis, Kanazawa 921-8001, Ishikawa, Japan; info@west-inter.or.jp
[35] Maro Clinic, Tanabe 646-0004, Wakayama, Japan; maroclinic339@gmail.com
[36] Nishijin Hospital, Kyoto 602-8319, Kyoto, Japan; koyama580@nisijin.net
[37] Department of Nephrology, Yamanashi Prefectural Central Hospital, Kofu 400-0027, Yamanashi, Japan; naganuma-bfpn@ych.pref.yamanashi.jp
[38] Department of Internal Medicine, Yuurinkouseikai Fuji Hospital, Gotemba 412-0043, Shizuoka, Japan; ogi@yuurinkouseikai.or.jp
[39] Katayama Clinic, Iwakuni 741-0072, Yamaguchi, Japan; ktclinic@bronze.ocn.ne.jp
[40] Mizue Yuai Clinic, Edogawa 133-0065, Tokyo, Japan; yuai@zuiko.or.jp
[41] Joetsu General Hospital, Joetsu 943-8507, Niigata, Japan; kamedash@joetsu-hp.jp
[42] Division of Nephrology and Hypertension, Department of Internal medicine, St. Marianna University Yokohama Seibu Hospital, Yokohama 241-0811, Kanagawa, Japan; sirababu@marianna-u.ac.jp
* Correspondence: tomosugi@kanazawa-med.ac.jp

Abstract: Oral ferric citrate hydrate (FCH) is effective for iron deficiencies in hemodialysis patients; however, how iron balance in the body affects iron absorption in the intestinal tract remains unclear. This prospective observational study (Riona-Oral Iron Absorption Trial, R-OIAT, UMIN 000031406) was conducted at 42 hemodialysis centers in Japan, wherein 268 hemodialysis patients without inflammation were enrolled and treated with a fixed amount of FCH for 6 months. We assessed the predictive value of hepcidin-25 for iron absorption and iron shift between ferritin (FTN) and red blood cells (RBCs) following FCH therapy. Serum iron changes at 2 h (ΔFe2h) after FCH ingestion were evaluated as iron absorption. The primary outcome was the quantitative delineation of iron variables with respect to ΔFe2h, and the secondary outcome was the description of the predictors of the body's iron balance. Generalized estimating equations (GEEs) were used to identify the determinants of iron absorption during each phase of FCH treatment. ΔFe2h increased when hepcidin-25 and TSAT decreased (−0.459, −0.643 to −0.276, $p = 0.000$; −0.648, −1.099 to −0.197, $p = 0.005$, respectively) in GEEs. FTN increased when RBCs decreased (−1.392, −1.749 to −1.035, $p = 0.000$) and hepcidin-25 increased (0.297, 0.239 to 0.355, $p = 0.000$). Limiting erythropoiesis to maintain hemoglobin levels induces RBC reduction in hemodialysis patients, resulting in increased hepcidin-25 and FTN levels. Hepcidin-25 production may prompt an iron shift from RBC iron to FTN iron, inhibiting iron absorption even with continued FCH intake.

Keywords: oral iron absorption; ferric citrate hydrate; hemodialysis; hepcidin-25; iron shift

1. Introduction

Patients undergoing hemodialysis lose 1.5–3.0 g of iron annually due to dialysis and periodic laboratory evaluations [1], leading to iron deficiency. The oral supplementation of ferrous iron is inconvenient for iron deficiency anemia in dialysis patients due to gastrointestinal side effects [2], while the use of highly soluble ferric citrate (FC) is increasing because it has fewer side effects [3]. The long-term administration of FC increases ferritin (FTN) and transferrin saturation (TSAT), reduces intravenous iron and erythropoiesis-stimulating agent (ESA) dose requirements, and maintains hemoglobin (Hb) levels in hemodialysis patients [4–6]. Nevertheless, it remains unclear what fraction of FC is absorbed, what type of iron state promotes iron absorption, and whether long-term FC administration causes iron overload.

FTN is an index of stored iron [7], but its appropriate value in the body remains unknown. There are large differences in FTN levels in hemodialysis patients across countries, with patients in Japan and the USA having the lowest and highest FTN levels, respectively [8]. It is speculated that if a large difference exists in the amount of iron stored, there will be a difference in iron absorption regulated by hepcidin-25; however, previous FC studies have reported the same phenomena [4,5]. Yokoyama et al. [4] found that FTN essentially plateaued at week 28, increasing from 57 ng/mL at baseline to 227 ng/mL after